Received: 16 December 2020 | Revised: 23 February 2021 | Accepted: 25 February 2021

DOI: 10.1111/apa.15821

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

REGULAR ARTICLE

Maternal autoimmune disease is not associated with cancer in the offspring

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Funding information
Dr. Seppälä received a research grant from Ida Montinin säätiö, Lastentautien tutkimussäätiö and Väreen säätiö for this study as a part of her PhD project. The funding bodies had no role in planning or conducting the study.

Abstract

Aim: Autoimmune disease and its medication are associated with increased cancer risk in adults, but it is unknown whether maternal autoimmune disease and/or medication use in pregnancy are associated with increased cancer risk in offspring.

Methods: In this case-control study, we identified all patients under 20 years of age with their first cancer diagnosis in 1996–2014 from the Finnish Cancer Registry (n = 2029) and 1:5 population-based controls (n = 10,103) from the Medical Birth Register. We obtained information on maternal autoimmune disease and its medication from the relevant Finnish registries and used conditional logistic regression to analyse the risk of offspring cancer after maternal autoimmune disease exposure.

Results: The odds ratio (OR) for cancer in offspring following maternal autoimmune exposure was 0.76 (95% confidence interval [CI] 0.47–1.23). Individual ORs for inflammatory bowel and connective tissue diseases were 1.08 (95% CI 0.56–2.01) and 0.50 (95% CI 0.23–1.08), respectively. The OR for maternal autoimmune medication was 0.95 (95% CI 0.80–1.14) overall and similar by drug subtype. There was an increased risk with medication in late pregnancy but the ORs were unstable owing to small numbers.

Conclusion: Our study does not support an increased cancer risk among offspring of women with autoimmune disease or its medication during pregnancy.

KEYWORDS
antenatal exposure, childhood cancer risk, maternal autoimmune disease, maternal medication, registry-based study

Key notes

- This study was conducted to determine whether maternal autoimmune disease and/or its medication, known to increase cancer risk in adults, are also associated with an increased childhood cancer risk among their offspring.
- In this population-based registry study, maternal autoimmune disease and/or its medication were not associated with an increased childhood cancer risk in the offspring.
- The possible protective results for maternal connective tissue disease warrant further research.

Abbreviations: CI, confidence interval; OR, odds ratio.

1 | INTRODUCTION

Autoimmune diseases, such as connective tissue or inflammatory bowel disease, affect women in their reproductive ages. In 0.7% of pregnancies ending in delivery in Finland, the mother receives reimbursement for drug therapy costs of a connective tissue disease. According to the Finnish Institute of Health and Welfare, inflammatory bowel disease is equally common among pregnant women.[1]

In Finland, up to 200 cancers are diagnosed annually among children and adolescents under 20 years of age. Cancer remains the most common, non-accidental cause of death among children in developed countries. The aetiology of childhood cancer is unclear with only 5–10% of cases linked to hereditary cancer predisposition syndromes and the same proportion possibly to yet undefined environmental factors.[2]

Autoimmune disease, especially rheumatoid arthritis, appears to increase the risk of cancer among adult patients.[3-6] Also, therapies used to treat autoimmune disease, such as TNF-alpha-inhibitors, have been associated with an increased risk. Both rheumatoid arthritis and its treatment have been associated with lymphoma.[7,8] There is speculation that the risk is positively associated with increasing severity of the disease.[5]

The relationship between a familial autoimmune disease and the risk of childhood cancer has been previously studied, mostly in case-control settings with the exposure data being based either on recall [3,9-11] or population-based registries.[12-15] Only one study reported a significant association between a maternal autoimmune disease, that is exposure in utero to the mother's condition, and childhood Hodgkin´s lymphoma.[3] The rest found positive but non-significant[11,12,14,15] associations or no association[9,10,13] between a maternal autoimmune disease and childhood acute lymphoblastic leukaemia (ALL) and lymphomas. The definition of autoimmune disease varied widely among the studies warranting a population-based approach with specific subgroups.

We investigated whether a maternal autoimmune disease or its medication are associated with the risk of cancer in the offspring up to the age of 20 years using national, population-based, registry data.

2 | MATERIALS AND METHODS

A unique personal identity code given to each Finnish citizen since 1967 allows for the linkage of information recovered from the health and vital statistics registries. Permanent residents of Finland are covered through the Finnish National Health Insurance and eligible for reimbursement for the cost of prescription medicines. People with certain chronic diseases are eligible for special reimbursement for their prescription medicine costs, and they are assigned a special reimbursement code.

The Finnish Cancer Registry started systematic, nationwide registration of cancer in 1953 and includes data on treatments and causes of death. It has a 95% coverage for all cancers.[16] The completeness for childhood cancer is 92% for solid tumours and 97% for leukaemia.[17]

The Finnish Medical Birth Register, run by the Finnish Institute for Health and Welfare, was founded in 1987. The Medical Birth Register contains data on all mothers who have delivered a child in Finland, and the obstetric and neonatal outcomes are available until seven days after delivery or at hospital discharge.

The Register of Reimbursed Drug Purchases is maintained by the Social Insurance Institute of Finland and retains data on all prescription drugs reimbursed since 1993. The database includes personal information on the Anatomic Therapeutic Chemical code of the drug, date of purchase, package size, drug cost and refund category.

The Care Register for Health Care is maintained by The Finnish Institute of Health and Welfare since 1969 and contains information on patients, hospital admissions and discharges, diagnoses and treatment given in secondary and tertiary health care.

Research permits were obtained from The Finnish Institute of Health and Welfare (THL/252/5.05.00/2016), Social Insurance Institute of Finland (15/52272016) and Helsinki University. No ethical board review was required as this study was based on national statutory registries, and no study participants were contacted.

2.1 | Study population

We identified all 2037 individuals with a first cancer diagnosis before the age of 20 years in the FCR for the years 1996–2014. We also identified five population-based controls for every case (n = 10,185) matched on sex and birth year from the Medical Birth Register. Due to missing data on birth weight, eight cases and 82 controls were excluded (Figure 1), resulting in 2029 cases and 10,103 controls being included in the analysis. For the descriptive characteristics of the cases and controls, see Table 1.

2.2 | Exposure definition and classification

The medical information on an autoimmune disease in the mother recorded any time before the delivery was obtained from the Care Register for Health Care, the Medical Birth Register and the Register of Medical Special Reimbursements. We extracted the diagnoses codes using the International Classification of Diseases Ninth Revision (ICD-9 codes 135, 446–447, 555–556, 696, 710, 714 and 720) and Tenth Revision (ICD-10 codes K50-K51, L40, M05-M09, M45-M49 and D86) and special reimbursement codes (132, 202 and 208). Due to small numbers for some diseases, two subgroups were formed a priori: mothers with an inflammatory bowel disease (ICD-9 codes 555–556, ICD-10 codes K50-K51 and special reimbursement code 208) and those with a connective tissue disease, including rheumatoid arthritis, ankylosing spondylitis, psoriasis, sarcoidosis and vasculitis (ICD-9 codes 135, 446–447, 696, 710, 714, 720, ICD-10 codes L40, M05-M09, M45-M49, D86 and special reimbursement codes 132 and 202).

Information on the medications that the mothers purchased three months prior to conception and/or during pregnancy was obtained from the Register of Reimbursed Drug Purchases. Medications used to treat the autoimmune disease were identified with the Anatomic Therapeutic Chemical code classification using the second- and third-level codes: intestinal anti-inflammatory agents used to treat inflammatory bowel disease medication, (A07E), systemic corticosteroids (H02), immunosuppressants (L04) and anti-inflammatory and antirheumatic products (M01). We analysed the associations for the autoimmune disease and medications separately, because the women with autoimmune disease may not purchase the medication, or alternatively women may purchase medication without a diagnosis in the registries. The dosage was not available to us in an analysable format.

The date of conception was calculated as the date of delivery minus gestational age at birth in days based on ultrasound or best clinical estimate if there was no ultrasound confirmation, as registered in the MBR. Birth weight for gestational age was categorised as small, appropriate or large for gestational age. Small for gestational age was defined as a birth weight under 2 SD, and large for gestational age as a birth weight over 2 SD of the standard, population-based growth curves.[18]

2.3 | Cancer definition and classification

Cancer was defined as a malignant neoplasm. We also included benign or borderline tumours of the central nervous system, for example, pilocytic astrocytomas, considered borderline, and the most common central nervous system tumour in childhood. The Finnish Cancer Registry uses the International Classification of Childhood Cancer: with morphology (ICD-O-3) and with morphology and site (ICCC3) (codes 011 for ALL, 011–015 for all leukaemia, 021–025 for lymphomas, 031–036 for CNS tumours and 037–122 for other cancers).[19]

2.4 | Statistical analysis

We evaluated the association between the autoimmune disease of the mother and risk of childhood cancer in her offspring using conditional logistic regression to estimate the odds ratios (OR) and 95% confidence intervals (CI). Models were performed for each autoimmune disease variable with cancer risk; any autoimmune disease diagnosis or medication; any autoimmune disease diagnosis; inflammatory bowel disease; rheumatic disease; any autoimmune disease medication; systemic corticosteroids; immunosuppressants; anti-inflammatory and antirheumatic products. The model was then repeated adjusting for maternal age categorised to those under 25 years, 25–29 years or 30 years or older. Other adjustment criteria were parity, categorised as primiparous or multiparous and maternal smoking status during pregnancy. To account for the incomplete information on smoking status, we employed a complete case approach restricting the analysis to those without missing data.

We then considered multiple sensitivity and secondary analyses. Both low and high birth weight have been associated with childhood

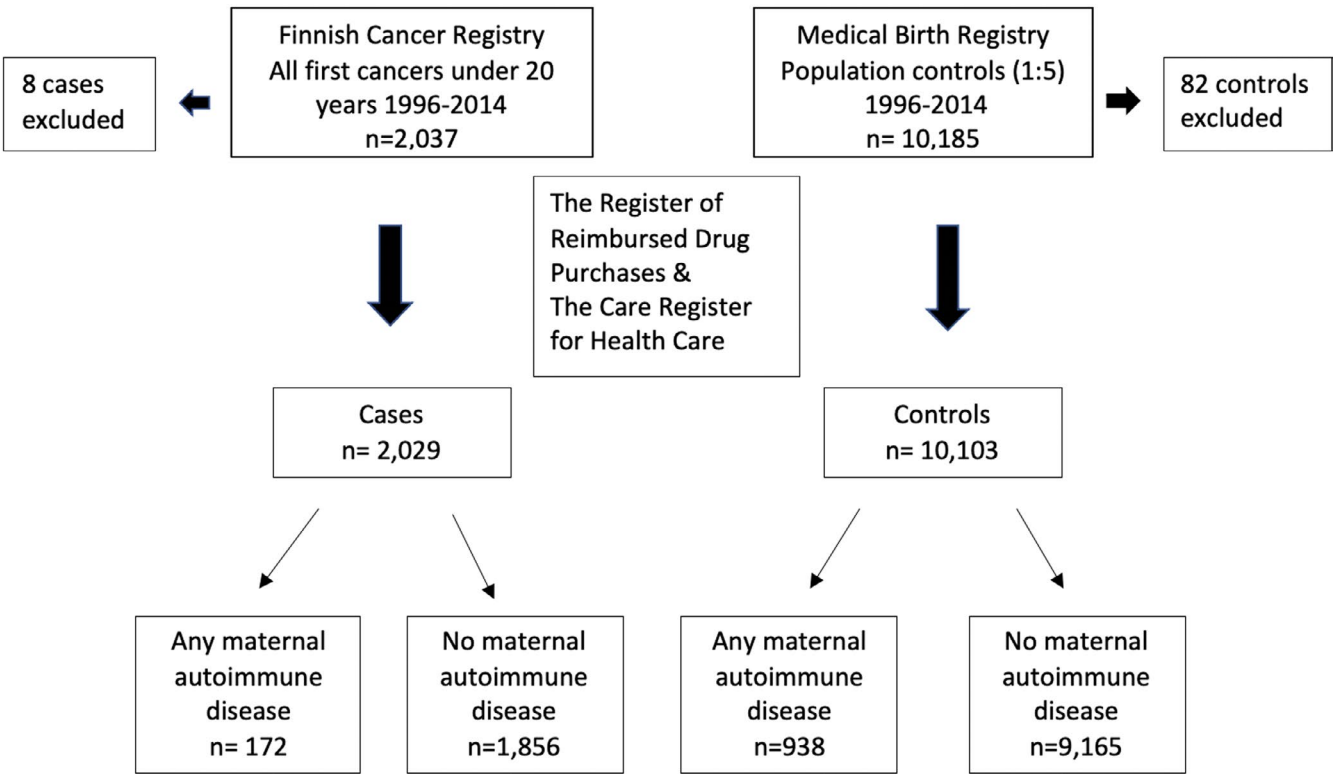

FIGURE 1 Flow chart of case-control data formation, 1996–2014. 8 cases and 82 controls were excluded due to missing information on birth weight of gestational age

TABLE 1 Maternal and offspring characteristics of childhood cancer cases and controls, 1996–2014

	Number of cases 2029	Percentage of cases	Number of controls 10,103	Percentage of controls
Maternal characteristics				
Maternal age (years)				
<25	355	17.5	1872	18.5
25–29	639	31.5	3246	32.1
≥30	1035	51.0	4985	49.3
Parity				
Primiparous	847	41.7	4098	40.6
Multiparous	1182	58.3	6005	59.4
Maternal smoking				
Yes	291	14.3	1447	14.3
No	1680	82.8	8404	83.1
Unknown	58	2.9	252	2.5
A diagnosis of autoimmune disease prior to delivery	19	0.9	134	1.3
Any autoimmune disease medication purchase 3 months before/during pregnancy (ATC-code)	169	8.3	888	8.8
Inflammatory bowel disease medication (A07E)	13	0.6	65	0.6
Systemic corticosteroids (H02)	21	1.0	107	1.1
Immunosuppressants (L04)	3	0.1	13	0.1
Anti-inflammatory and antirheumatic products (M01)	141	6.9	761	7.5
Inflammatory bowel disease	12	0.6	61	0.6
Inflammatory bowel disease diagnosis, no medication	2	0.1	12	0.1
Connective tissue disease	7	0.3	74	0.7
Connective tissue disease diagnosis, no medication	1	0.05	38	0.4
Offspring characteristics				
Offspring sex				
Male	1092	53.8	5431	53.8
Female	937	46.2	4672	46.2
Multiple pregnancy				
No	1962	96.7	9784	96.8
Yes	67	3.3	319	3.2
Gestational age				
<37 weeks	141	6.9	537	5.3
≥37 weeks	1888	93.1	9566	94.7
Weight for gestational age (size at birth)				
Small for gestational age	55	2.7	217	2.1
Appropriate for gestational age	1881	92.7	9587	94.9
Large for gestational age	93	4.6	299	3.0
Delivery type				
Vaginal birth	1675	82.6	8470	83.8
Caesarean section	354	17.4	1627	16.1
Unknown	0	0.0	6	0.5

cancer risk,[20,21] and mothers with an autoimmune disease are known to deliver smaller babies.[22,23] Thus, birth weight is potentially a mediator of the relationship between a maternal autoimmune disease and the offspring cancer risk. To account for this, we conducted a sensitivity analysis adjusting birth weight for gestational age. We also performed subgroup analyses limited to cases diagnosed with specific childhood cancers. To evaluate the role of matching, we performed a stratified sensitivity analysis with unmatched data for birth year and gender. To estimate the impact of non-specific analgesics on the overall association, we performed a sensitivity analysis for autoimmune disease medication excluding the anti-inflammatory and antirheumatic products. We also analysed data on medication by stratifying the drug purchases into two groups: those during the three months before pregnancy and/or during the first trimester, and those during the second and, or, third trimester. Women on medication throughout pregnancy contributed to both categories. The statistical analyses were performed with the STATA MP14 (StataCorp LLC).

3 | RESULTS

A total of 172 (8.5% of 2029) cases with cancer and prenatally exposed to any maternal autoimmune disease and the medication used as disease therapy were included. Sixteen cases (0.8% of all cases) had a mother with an autoimmune disease diagnosis and used medication, three (0.1% of all cases) had a diagnosis but no medication, and 150 (7.4% of all cases) had medication but not a diagnosis. In the control group, there were 938 (9.3% of 10,103 controls) offspring exposed to maternal autoimmune disease and, or, its medication. Eighty-five mothers (0.8% of all controls) had a diagnosis of autoimmune disease and used medication, 50 mothers (0.5% of all controls) had a diagnosis but no medication, and 753 (7.5% of all controls) had medication but not a diagnosis.

The maternal autoimmune diseases included in the analyses were not associated with an increased risk for offspring cancer (crude OR 0.70, 95% CI 0.43–1.14) when compared to the offspring of mothers with no autoimmune disease. This result was similar after adjusting for maternal age, parity and smoking status (OR 0.76, 95% CI 0.47–1.23) or when further adjusted for birth weight for gestational age (OR 0.76, 95% CI 0.47–1.24). For inflammatory bowel disease, the adjusted OR was 1.08 (95% CI 0.56–2.01) and 0.50 (95% CI 0.23–1.08) for the connective tissue diseases (Table 2).

The results remained unaltered in an unmatched analysis stratified by birth year and sex (adjusted OR for any autoimmune disease 0.70, 95% CI 0.43–1.15), except for a maternal connective tissue disease showing a lower risk for childhood cancer (OR 0.41, 95% CI 0.18–0.94) (Table S1). There was no change in the results in a sensitivity analysis with further adjustment for the birthweight (data not shown).

Any maternal medication used to treat the autoimmune disease and purchased up to three months before or during the pregnancy was not associated with an increased risk of childhood cancer (adjusted OR 0.95, 95% CI 0.80–1.14). The results by the class of drugs were similar: maternal inflammatory bowel disease medication (adjusted OR 1.08, 95% CI 0.59–1.97), systemic corticosteroids (adjusted OR 1.01, 95% CI 0.64–1.63), immunosuppressants (adjusted OR 1.28 with 95% CI 0.36–4.60) or anti-inflammatory

TABLE 2 Maternal autoimmune disease, its medication and the risk of childhood cancer in the offspring, compared to healthy controls, 1996–2014

	Number of cases (%)	Number of controls (%)	OR[a]	95% CI	OR[b]	95% CI
No autoimmune disease	2010 (99.1)	9969 (98.7)	1.00	—	1.00	—
Any autoimmune disease-related exposure (diagnosis or medication)	172 (8.5)	938 (9.3)	0.91	0.76–1.08	0.92	0.77–1.09
Any autoimmune disease diagnosis	19 (0.9)	134 (1.3)	0.70	0.43–1.14	0.76	0.47–1.23
Inflammatory bowel disease	12 (0.6)	61 (0.6)	0.98	0.53–1.82	1.08	0.56–2
Connective tissue disease	7 (0.3)	74 (0.7)	0.47	0.21–1.02	0.50	0.23–1.0
No autoimmune disease medication purchases	1860 (91.7)	9215 (91.2)	1.00	—	1.00	
Any autoimmune disease medication purchase	169 (8.3)	888 (8.8)	0.95	0.80–1.12	0.95	0.80–1.14
Inflammatory bowel disease medication	13 (0.6)	65 (0.6)	0.97	0.55–1.81	1.08	0.59–1.97
Systemic corticosteroids	21 (1.0)	107 (1.1)	0.98	0.61–1.57	1.01	0.64–1.63
Immunosuppressants	3 (0.1)	13 (0.1)	1.15	0.33–4.05	1.28	0.36–4.60
Anti-inflammatory and antirheumatic products	141 (6.9)	761 (7.5)	0.92	0.76–1.11	0.92	0.76–1.11

[a]From conditional logistic regression models without adjustment.

[b]From conditional logistic regression models that included maternal age (categorised), parity and smoking status

TABLE 3 Maternal autoimmune disease and its medication in offspring with childhood cancer subtypes, compared to healthy controls, 1996–2014

Cancer subtypes	Number of cases (%)	Crude OR[a]	95% CI	OR[b]	95% CI
Any maternal autoimmune disease					
No autoimmune disease		1.00	—	1.00	—
All leukaemia	6 (0.2)	0.69	0.29–1.63	0.72	0.30–1.71
Acute lymphoblastic leukaemia	5 (0.2)	0.78	0.30–2.01	0.84	0.32–2.19
Lymphomas	1 (0.04)	0.71	0.09–5.81	0.80	0.09–6.80
Central nervous system tumours	8 (0.4)	1.29	0.59–2.81	1.44	0.65–3.19
Other cancers[c]	4 (0.2)	0.37	0.13–1.04	0.41	0.15–1.13
Any maternal autoimmune disease medication					
No autoimmune disease medication purchases		1.00	—	1.00	—
All leukaemia	55 (2.7)	0.88	0.65–1.19	0.85	0.63–1.16
Acute lymphoblastic leukaemia	45 (2.2)	0.97	0.69–1.35	0.93	0.66–1.32
Lymphomas	14 (0.7)	1.29	0.70–2.38	1.32	0.70–2.48
Central nervous system tumours	40 (2.0)	1.01	0.71–1.44	1.01	0.70–1.45
Other cancers[c]	60 (3.0)	0.91	0.69–1.22	0.94	0.71–1.26

[a]Odds ratio (OR) and 95% confidence interval (CI) from conditional logistic regression models without adjustment.

[b]OR and 95% CI from conditional logistic regression models that included maternal age (categorised), parity and smoking status.

[c]Other cancers including non-CNS and all cancers not categorised to other subgroups.

and antirheumatic products (adjusted OR 0.92, 95% CI 0.76–1.11) compared with no medication (Table 2). In a sensitivity analysis for any maternal autoimmune disease medication excluding the anti-inflammatory and antirheumatic products, the adjusted OR was 1.06 (95% CI 0.72–1.56, data not shown).

Analyses by cancer subtype (Table 3) also generally showed results compatible with no association between a maternal autoimmune disease and childhood cancer in the offspring. We found no association with acute lymphoblastic leukaemia (adjusted OR for maternal autoimmune disease 0.72, 95% CI 0.30–1.71, for medication OR 0.93, 95% CI 0.66–1.32) nor for lymphomas (adjusted OR for autoimmune disease medication 0.80, 95% CI 0.09–6.80). However, an increased, but not statistically significant OR for lymphomas with autoimmune disease medication was observed (adjusted OR 1.32, 95% CI 0.70–2.48).

In analyses by trimester, the adjusted OR was 0.89 (95% CI 0.73–1.09) for cancer risk associated with autoimmune disease medication before and/or during the first trimester, and 1.32 (95% CI 0.74–2.44) for the second and/or third trimesters (Table S2). The same pattern was observed in subgroup analyses for the use of corticosteroids or anti-inflammatory and antirheumatic products Table S3 and Table S4.

4 | DISCUSSION

We found no definitive evidence of increased cancer risk among the offspring of women with an inflammatory bowel disease or connective tissue disease during pregnancy, compared with mothers with no autoimmune disease. These results are in line with previous publications.[9,10,13]

Maternal connective tissue diseases, including rheumatoid arthritis, however, appeared to be associated with a lower risk of childhood cancer as shown in stratified analysis. A lower risk for childhood acute lymphoblastic leukaemia has been demonstrated only for rheumatoid arthritis in one previous study with self-reported data,[10] but the underlying biology remains unclear. This warrants repeating the analysis for rheumatoid arthritis in a larger study and possibly further exploring the biology.

Our findings were not consistent with an increased risk of childhood leukaemia or lymphomas following maternal autoimmune disease exposure as previously shown by some,[3,23] but not all studies.[9-12,14,15] The impact on risk for cancers other than leukaemia or lymphomas also remains inconclusive, with positive associations in other studies possibly due to varying definitions of autoimmune disease, for example, including maternal diabetes which is known to be associated with childhood cancer.[24,25] This emphasises the need for prospective collection of detailed and standardised data for future analyses.

Biological, including genetic, explanations for the associations of maternal autoimmune disease or its medication with the risk of cancer in the offspring are unknown. Yet, there is an established risk of cancer, particularly the lymphomas, among the adult patients with an autoimmune disease.[5,6,12,26] The cases were younger than 20 years of age in our study, so we cannot rule out a possible increase in cancer risk later in life.

Maternal autoimmune disease and resulting glucocorticoid stress was not a risk factor for childhood cancer in our study.[27] Autoimmune disease medication can partially cross the placenta and is associated with an elevated risk of malformations. Despite this, it was not associated with childhood cancer in the offspring.[7,28]

Our subgroup analysis by trimester, however, suggested a potentially harmful impact rendered by autoimmune medication later in pregnancy, for corticosteroids as well as anti-inflammatory and antirheumatic products. Unfortunately, we lacked data on steroids administered antenatally at the hospital, shown previously to be associated with an increased childhood cancer risk.[29] In our sensitivity analysis without the anti-inflammatory medication, the OR for autoimmune disease medication was slightly higher, indicating a need for more detailed analysis on the different autoimmune disease medication groups. Medication used to treat autoimmune disease changed markedly during the study period and thereafter with targeted biological therapies being currently available. In addition, we were unable to separate the immunosuppressive medication into subgroups. This and the trimester-specific impact of autoimmune disease medication on cancer risk of the offspring warrants further investigation also including therapy given in the hospital (antenatal steroids) and the other maternal autoimmune diseases not covered in this study.

4.1 | Strengths and limitations

The use of detailed and comprehensive data on maternal autoimmune disease medication is a strength of our study. Additional strengths include the population-based and nationwide structure of our national registry data with standardised definitions of the exposure and outcome.

We found the use of relevant medications among pregnant mothers to be eight times more prevalent than the actual diagnosis of an autoimmune disease, likely due to other indications for some of the medications, especially analgesics. Some of the medication in this group of anti-inflammatory and antirheumatic products can also be bought without prescription in Finland, most likely resulting in the capture of drug utilisation in this group being incomplete. Furthermore, our data were solely based on drug purchase information and did not include data on dosage. We were also limited by small numbers especially for the cancer subtypes, especially for the evaluation of medications by trimester.

5 | CONCLUSION

In our population- and registry-based, nationwide dataset, we did not find the risk of childhood cancer, or its key subtypes, to be increased following exposure to a maternal autoimmune disease and, or, its medication. Whether the risk is impacted by the status of the foetal development (trimester) remains unclear. The possible protective association with connective tissue disease, especially rheumatoid arthritis, warrants confirmation.

ACKNOWLEDGEMENTS

Dr. Seppälä would like to thank Ida Montinin säätiö, Lastentautien tutkimussäätiö and Väreen säätiö for personal grants.

CONFLICT OF INTEREST

The authors report no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Seppälä LK, Madanat-Harjuoja L-M, Troisi R, Sampson JN, Leinonen MK, Vettenranta K. Maternal autoimmune disease is not associated with cancer in the offspring. *Acta Paediatr*. 2021;110:2259–2266. https://doi.org/10.1111/apa.15821