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Maternal autoimmune disease and its association with childhood cancer: A population-based case-control study in Denmark

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ABSTRACT

Background: Autoimmune diseases have been linked to an increased risk of pregnancy-related complications. A family history of autoimmune diseases may be related to the risk of childhood cancer based on similar histocompatibility antigens. We utilized data from national registries in Denmark to examine associations between maternal autoimmune disease and cancer in their offspring.

Methods: We linked data from several national registries in Denmark to identify childhood cancer cases in children <20 years diagnosed between 1977 to 2016. Controls were selected from the Central Population Register and matched to cases by birth year and sex (25:1). Mothers with autoimmune disease diagnosed in pregnancy or prior were identified from the National Patient Register. Multivariable conditional logistic regression analyses were used to estimate associations between maternal autoimmune diseases and childhood cancer in offspring.

Results: Autoimmune diseases (all types) were positively associated with all childhood cancers combined (Odds Ratio (OR) = 1.25, 95% CI 1.06, 1.47), acute lymphoblastic leukemia (OR =1.52, 95% CI 1.09, 2.13), Burkitt lymphoma (OR = 2.69, 95% CI 1.04, 6.97), and central nervous system tumors (OR = 1.45, 95% CI 1.06, 1.99), especially astrocytoma (OR = 2.27, 95% CI 1.36, 3.77) and glioma (OR = 1.75, 95% CI 1.13, 2.73). When we examined mothers with rheumatoid arthritis, we observed an increased association for all cancers (OR = 2.15, 95% CI 1.40, 3.30), acute lymphoblastic leukemia (OR = 3.55, 95% CI 1.69, 7.47), and central nervous system tumors (OR = 2.91, 95% CI 1.46, 5.82), especially glioma (OR = 3.58, 95% CI 1.40, 9.18) in offspring.

Conclusion: There is a positive association between maternal autoimmune disease and childhood cancer. This association is especially prominent in the offspring of women with rheumatoid arthritis.

1. Background

Cancer is the leading disease-causing death in children, only surpassed by accidents in child and adolescent mortality. Risk factors reported to play roles in cancer development among children include lifestyle, occupational, and environmental factors such as radiation exposure, air pollution, genetic mutations, and cancer-linked genetic disorders. There is increasing evidence that maternal chronic conditions in pregnancy, and associated medication use, may impact risk of pediatric cancers [1–4].

Autoimmune disorders cause the immune system to attack multiple organs in the body due to an inability of the immune system to differentiate the host cells from foreign cells [5]. Autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, Type-1 diabetes, multiple sclerosis, and scleroderma are often associated with severe morbidity and mortality. During pregnancy, the body undergoes hormonal changes, and fetal antigens can serve as a trigger for the development of autoimmune diseases [5]. One in twelve women in the United States will develop some autoimmune disease during their lifetime, versus only one in twenty men. Approximately 3.6% of women in the

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United States have been diagnosed with rheumatoid arthritis. Rheumatoid arthritis can impact pregnancy via reduced fertility and lead to an increased risk of complications such as neurodevelopmental disorders, preterm birth, miscarriage, and preeclampsia [6,7]; both preeclampsia and preterm birth have been linked to childhood cancer [8]. Autoimmune diseases are associated with cardiovascular diseases and cesarean delivery [9], which may also be related to childhood cancer.

A few epidemiological studies have suggested an increased risk of hematological cancers in children born to parents with autoimmune diseases [10–15], specifically associations between multiple sclerosis and acute leukemia [10], autoimmune thyroiditis (Graves' disease), Hashimoto's thyroiditis and leukemia [12], and systemic lupus erythematosus in mothers and non-Hodgkin's lymphoma in offspring [16]. However, not all studies have shown increased risks [2,17]. Varying results may be due to the etiologic heterogeneity of hematologic subtypes, the age of onset of leukemia, or the small number of exposed cases in most studies.

Given the small number of studies and inconsistent results, we examined autoimmune disease and its association with childhood cancer in a population-based study in Denmark using national individual medical and pharmaceutical records, which can all be linked by the use of a unique personal identifier applied to residents since 1968.

2. Materials and Methods

Childhood cancer cases were identified from the Danish Cancer Registry, established in 1942, which contains information on morphology, topography, and date of diagnosis, among other factors [18]. The diagnosis was based on the International Classification of Diseases (ICD-7) until 1977, thereafter ICD-O, and from 2004 ICD-10 afterward; the subtype of cancer was based on morphology recorded in the International Classification of Childhood Cancer (ICCC) revision one until 2003 and revision three subsequently [19]. We included all cancer cases born in Denmark between 1977 (the first year of the National Patient Register) and 2013, aged 0–19 years at diagnosis, and diagnosed between 1977 and 2016. Cases included all tumors with malignant behavior and malignant and non-malignant tumors of the central nervous system.

Controls born in Denmark, randomly selected from the Central Population Registry [20], were matched by birth date and sex (ratio 1:25) and were free of cancer at the date of diagnosis of the corresponding case. Children who were likely not viable (gestational age ≤ 20 weeks or birth weight < 500 g, $n = 17$) were excluded, resulting in 6420 cases and 160,484 controls for the final analyses.

The cases and controls were linked to the Medical Births Registry [21] for gestational information. We used ICD codes to determine mothers diagnosed with autoimmune diseases up to 4 years after birth, which takes into account the preclinical phase of disease [22]. Data on maternal autoimmune diagnoses were retrieved from the Danish National Patient Registry (1977–2016), using International Classification of Disease codes (ICD-8 codes during 1977–1993 and ICD-10 codes from 1994), using ICD codes identified by Eaton and colleagues [23]. We previously examined Type-1 diabetes in relation to childhood cancer [1]; therefore, we included it here among all autoimmune diseases, but we did not report on it individually (please note that the ICD codes used in our previous analysis [1] differ slightly than those in Eaton's manuscript [23]; for consistency in the present analysis we are using Eaton's ICD coding).

Multivariable conditional logistic regression analyses were used to estimate associations with maternal autoimmune diseases and childhood cancer in offspring. We limited analyses to cancer types with at least five exposed cases. We first examined the relationship between rheumatoid arthritis and childhood cancer. We attempted to investigate other types of autoimmune diseases, but power was limited, except for inflammatory bowel disease and psoriasis, which we reported on in exploratory analyses. Second, to compare our results to earlier studies, we examined the association between any maternal autoimmune disease (all types combined) and childhood cancer. Finally, to determine whether observed associations were solely due to rheumatoid arthritis, we examined associations for any maternal autoimmune disease other than rheumatoid arthritis.

The covariates were selected based on the literature [11] and obtained from the Medical Birth Register. All models were adjusted for maternal age (continuous) and maternal history of cardiovascular disease (ICD-8 code 425.99 and ICD-10 codes I42.0–43.8 or O90.3) [24] prior to the index child's birth (ever/never; Supplemental Figure 1). Other covariates were considered for inclusion based on the literature but left out of final models due to not meeting the 10% change in estimate criterion [25] were urban or rural residence, maternal birthplace (Denmark/other), parity, maternal history of infections during pregnancy [26] (ICD codes available in Supplemental Table 1), and the child's history of rheumatoid arthritis or other autoimmune disorders prior to cancer diagnosis. We did not adjust for cesarean section because it is a likely intermediate on the cancer pathway. Additionally, mediation analyses were conducted to evaluate the potential mediation effects of preterm birth and maternal pre-eclampsia during pregnancy, considering that they have both been linked to childhood cancer [8]. All statistical analyses were conducted using SAS, Version 9.4 (SAS Institute Inc., Cary, NC, USA).

Some antirheumatic drugs may be teratogenic; their potential impact on offspring cancer risk is unknown. Conversely, discontinuing effective therapy may result in disease relapse and a subsequent increase in the risk of adverse pregnancy outcomes. Thus, in a sensitivity analysis, we examined the National Pharmaceutical Register (established in 1996) for medications linked to rheumatoid arthritis to determine whether results changed when mothers redeemed prescriptions for these medications. Medications used for rheumatoid arthritis included azathioprine (L04AX01), methotrexate (L01BA01), leflunomide (L04AA13), sulfasalazine (A07EC01), hydroxychloroquine (P01BA02), etanercept (L04AB01), adalimumab (L04AB04), certolizumab pegol (L04AB05), tocilizumab (L04AC07), sarilumab (L04AC14), abatacept (L04AA24), infliximab (L04AB02), golimumab (L04AB06), rituximab (L01XC02), tofacitinib (L04AC07), baricitinib (L04AA37), and upadacitinib (L04AA44). Although 0.5% of mothers took any of these medications before pregnancy, less than five case mothers redeemed prescriptions for these medications during pregnancy; thus, medication intake was not used as a variable in analyses.

3. Results

Some of the most prevalent autoimmune disorders in this study include type I diabetes, rheumatoid arthritis, thyrotoxicosis, psoriasis, inflammatory bowel disease (Crohn's disease & ulcerative colitis), iridocyclitis, lupus, and celiac disease.

Demographic and maternal characteristics are displayed in Table 1. Mothers of cases were more often ages 35 and older and more often resided in urban areas and had a pre-pregnancy BMI > 25 compared to controls.

Demographic characteristics of the mothers with and without autoimmune diseases are shown in Supplemental Table 2. A higher proportion of mothers with autoimmune diseases were 30 years and above than those without. In addition, a higher percentage of mothers with autoimmune disorders lived in urban areas and were born in non-Western countries compared to mothers without autoimmune diseases. Mothers with autoimmune diseases had more bacterial infections in pregnancy, cardiovascular diseases before or during pregnancy, and more births via Cesarean section, compared to women without autoimmune diseases.

When examining mothers with any autoimmune disease, we observed an increased association with childhood cancer in the offspring, which was seen with all cancers (combined) OR = 1.25, 95% CI 1.06, 1.47), acute lymphoblastic leukemia (ALL; OR = 1.52, 95% CI 1.09, 2.13), Burkitt lymphoma (OR = 2.69, 95% CI 1.04, 6.97), central

Table 1
Childhood cancer in relation to demographic factors (birth year ≥1977).

Demographic or health factor	Cases N = 6420 n (%)	Controls N = 160484 n (%)
Maternal age group (years)		
< 25	1423 (22.2)	36,923 (23.0)
25-29	2472 (38.5)	60,759 (37.9)
30-34	1744 (27.2)	44,546 (27.8)
35-39	669 (10.4)	15,695 (9.8)
40 +	112 (1.7)	2561 (1.6)
Urbanicity of residence		
Urban	2114 (32.9)	50,981 (31.8)
Small town	1808 (28.2)	46,632 (29.1)
Rural	2498 (38.9)	62,871 (39.2)
Mother's birthplace		
Denmark	5853 (91.3)	146,777 (91.6)
Other Europe or North America	217 (3.4)	5523 (3.4)
Other	338 (5.3)	7893 (4.9)
Maternal smoking at the first prenatal visit[a]	818 (23.9)	20,753 (24.2)
Pre-pregnancy BMI[b]		
<18.5	33 (4.1)	815 (4.1)
18.5 – 25	496 (61.0)	12,775 (64.2)
25 – 30	181 (22.3)	4036 (20.3)
30 +	103 (12.7)	2273 (11.4)
Bacterial infection in pregnancy	125 (1.9)	2411 (1.5)
Viral infection in pregnancy	17 (0.3)	380 (0.2)
Cardiovascular disease, diagnosed before or during pregnancy	185 (2.9)	3945 (2.5)
Diabetes, diagnosed before or during pregnancy	84 (1.3)	1790 (1.1)
Index child born by cesarean section	815 (12.7)	17,647 (11.0)

[a] Maternal smoking was collected for the years 1991–1996 and 1998 +
[b] Pre-pregnancy BMI was collected for the years 2004 +

nervous system tumors (CNS; OR = 1.45, 95% CI 1.06, 1.99), especially astrocytoma (OR = 2.27, 95% CI 1.36, 3.77) and gliomas (OR = 1.75, 95% CI 1.13, 2.73) (Table 2).

The association between mothers with any autoimmune disease and cancer risk in offspring was not mediated by maternal pre-eclampsia during pregnancy and weakly mediated by preterm birth, as the mediated percentages for pre-eclampsia were both below 1% and those for preterm birth were –6.36% and 1.01%, respectively, assuming either there was an interaction with any autoimmune disease or not.

Considering mothers with rheumatoid arthritis, the sample size was more limited, but we estimated an increased risk of all cancers (OR = 2.15, 95% CI 1.40, 3.30), ALL (OR = 3.55, 95% CI 1.69, 7.47), CNS tumors (OR = 2.91, 95% CI 1.46, 5.82), and gliomas (OR = 3.58, 95% CI 1.40, 9.18) (Table 3). When excluding rheumatoid arthritis and examining the association with all other autoimmune conditions (combined), we only observed an association with astrocytoma (OR = 2.07, 95% 1.19, 3.60) (Supplemental Table 3).

Although most other autoimmune diseases were rare in our population, two different types of autoimmune conditions were sufficiently represented (exposed cases ≥ 5) to examine associations with childhood cancer. There was no increased association with cancer in offspring when mothers had been diagnosed with inflammatory bowel disease, either with regards to all cancers combined (OR = 1.19, 95% CI = 0.87, 1.62) or ALL (OR = 1.48, 95% CI = 0.78, 2.81). In addition, a slight increase in association with cancer was seen among mothers diagnosed with psoriasis (OR=1.59, 95% CI= 0.96, 2.65; for all cancer types combined).

Table 2
Maternal autoimmune disease (any type) and association with childhood cancer.

Type of Cancer	N (%)	Crude OR (95% CI)	*Adjusted OR (95% CI)
Controls	3060 (1.9)	Referent	Referent
All cancers	153 (2.4)	1.26 (1.07, 1.49)	1.25 (1.06, 1.47)
Acute lymphoblastic leukemia	38 (3.1)	1.55 (1.11, 2.16)	1.52 (1.09, 2.13)
Acute myeloid leukemia	7 (2.8)	1.44 (0.66, 3.12)	1.42 (0.66, 3.09)
Hodgkin lymphoma	6 (1.7)	1.11 (0.49, 2.56)	1.09 (0.48, 2.51)
Non-Hodgkin lymphoma	6 (1.9)	1.05 (0.46, 2.41)	1.05 (0.46, 2.40)
Burkitt lymphoma	5 (4.9)	2.77 (1.07, 7.15)	2.69 (1.04, 6.97)
Central nervous system tumors	43 (2.7)	1.45 (1.06, 1.99)	1.45 (1.06, 1.99)
Astrocytoma	17 (3.4)	2.22 (1.33, 3.68)	2.27 (1.36, 3.77)
Glioma	22 (2.8)	1.74 (1.12, 2.70)	1.75 (1.13, 2.73)
Intracranial and intraspinal embryonal tumor	12 (1.8)	1.08 (0.60, 1.95)	1.07 (0.59, 1.92)
Neuroblastoma	7 (2.6)	1.35 (0.62, 2.93)	1.34 (0.62, 2.90)
Wilms tumor	7 (3.5)	1.75 (0.80, 3.84)	1.83 (0.83, 4.02)

* Adjusted for maternal age and maternal history of cardiovascular disease before or during pregnancy.

Table 3
Maternal rheumatoid arthritis and association with childhood cancer.

Type of cancer	N (%)	Crude OR (95% CI)	*Adjusted OR (95% CI)
Controls	265 (0.2)	Referent	Referent
All cancers	23 (0.4)	2.17 (1.42, 3.33)	2.15 (1.40, 3.30)
Acute lymphoblastic leukemia	8 (0.7)	3.58 (1.71, 7.52)	3.55 (1.69, 7.47)
Central nervous system tumors	9 (0.6)	2.90 (1.45, 5.79)	2.91 (1.46, 5.82)
Glioma	5 (0.6)	3.50 (1.37, 8.98)	3.58 (1.40, 9.18)

* Adjusted for maternal age and maternal history of cardiovascular disease before or during pregnancy.

4. Discussion

This register-based nested case-control study of childhood cancer suggests that hospitalization for maternal autoimmune disease is related to an increased risk of cancer in children. While rheumatoid arthritis was strongly linked to all cancers, ALL, CNS, and gliomas, other types of autoimmune disorders in mothers were also associated with childhood cancer, although we lacked statistical power to examine most of these conditions individually. Our findings support other studies that show associations between a family history of autoimmune diseases and hematological cancers in offspring [10,12] and build on these prior results by discovering possible associations with different cancer types, such as CNS tumors. We observed possible associations between neuroblastoma and maternal autoimmune disease, potentially due to pleiotropic genes [27]. Links with Burkitt lymphoma may be due to Epstein-Barr virus, a potential cause of several autoimmune diseases [28].

Previous studies investigating childhood cancers in relation to rheumatoid arthritis have examined various cancer types [13,15]. One study found a positive association between maternal rheumatoid arthritis and the risk of lymphoma in young adults [15]. A Finnish register-based study showed results that are discrepant to ours,

observing no association between maternal autoimmune disease diagnosis and childhood cancer (all types combined); however, similar to our study, they observed a weak increased association with CNS tumors [17]. One reason for these differences might be that paper did not report specifically on rheumatoid arthritis diagnoses; instead, it reported on people taking antirheumatic drugs, and intake of those medications may have dropped in pregnancy, as we observed. Pregnant women have lower medication adherence, which would bias results in that study to the null. In addition, antirheumatics are also taken for other conditions, such as cancers, suggesting that antirheumatic medication intake may not be a good proxy for rheumatoid arthritis. A different case-control study that relied on self-report of autoimmune disorders found no associations with offspring ALL or acute myeloid leukemia [13].

The course of rheumatoid arthritis changes through pregnancy insofar that half of all pregnant women with rheumatoid arthritis have a decreased disease activity, and up to 40% have remission during the third trimester of pregnancy, after which 20% of women experience worse flare-ups postpartum [28]. Although antenatal use of some autoimmune medications, such as anti-Tumor Necrosis Factor inhibitors, has been reported to have low teratogenic risks, others, like methotrexate, have high teratogenic risks. Therefore, guidelines in Denmark and other countries recommend discontinuing confirmed teratogens before pregnancy and other non-teratogenic medications around 24–26 weeks of gestational age [28]. Our analysis determined that few mothers filled prescriptions for autoimmune medicines during pregnancy; thus, we could not assess any putative associations with medication intake.

In patients with rheumatoid arthritis and other autoimmune diseases, infections are a leading cause of morbidity, mortality and a common cause of hospital admission. These infections are commonly caused by opportunistic microorganisms [29]. Infections may be related to an increased risk of childhood cancer [30]; however, adjustment for pregnancy infections did not change our results. The predisposition of people with autoimmune disease to have an increased risk of infection and multimorbidity makes them more likely to take several medications simultaneously [31]. However, it is unclear if the other medicines they take for other conditions may play any role in the increased associations in offspring. Few studies have linked medications used during pregnancy to cancer in offspring, but suggestive findings have been seen with some types of medication [32].

Several plausible mechanisms may explain how maternal autoimmune diseases may be related to an increased association with childhood cancers in offspring. A study investigating changes in the epigenetics of white blood cells of children born to mothers with rheumatoid arthritis compared to the general population reported different DNA methylation patterns at cytosine-phosphate-guanine (CpG) sites in children born to parents with rheumatoid arthritis indicating varying genome-wide DNA methylation patterns. For example, CpG sites with differences in DNA methylation were associated with the decreased expression of the *ADD2* gene (ß-adductor protein) [33]. Changes in this protein have been associated with cancer pathogenesis and systemic lupus erythematosus [34].

The relationship between autoimmune diseases and cancers might be due to B-cell hyperactivity without normal T-cell control [14]. For example, childhood cancers in offspring of mothers with autoimmune diseases may stem from an aberrant immune system composition and response resulting in abnormal B-cell activation due to persistent antigenic stimulation, cell-cycle deregulation, and impaired apoptosis, which may result in uninhibited cell proliferation, increased humoral immune response, and risk of oncogene translocation [35]. Also, increased malignancy has been reported in adults with autoimmune diseases [36].

Another plausible mechanism of the relationship between maternal autoimmune disease and childhood cancer may involve genetic factors related to the immune system. Investigators have reported an association between HLA-DRB1 * 04 alleles and a twofold increase in ALL risk in children [37]. Similarly, HLA-DRB1 * 04 alleles are genetic susceptibility factors for rheumatoid arthritis, conferring up to an 11-fold increase in rheumatoid arthritis risk [38]. Likewise, various alleles of the human leukocyte antigen (HLA) class I and class II have been associated with autoimmune diseases such as multiple sclerosis, Type 1 diabetes, rheumatoid arthritis, or celiac disease [39]. The studies above show similar genotypic variations in autoimmune diseases and cancers. A recent study also showed that some childhood cancers might be genetically close to autoimmune diseases [27].

In addition to small numbers of some cancers and specific autoimmune diseases, a limitation of this study is that information on autoimmune diseases was only available from hospital records.

A strength of our research design was that the study was population-based, with independent ascertainment of autoimmune disease based on medical records and not subject to recall bias. Validation studies using maternal interviews reported that only 44% of autoimmune diseases in parents could be confirmed in medical records [14]. The free, universal health care in Denmark also increases the likelihood that people with autoimmune conditions will be diagnosed. Validation studies for several diseases diagnosed in the Danish National Health Register suggest 75% to 90% agreement between the register and medical records [40]. For specific autoimmune diseases such as ulcerative colitis, rheumatoid arthritis, and inflammatory bowel disease, the validity was 90%, 59%, and 95% kappa agreement, respectively [41].

Many of the cancers and autoimmune diseases we studied were rare and thus resulted in small sample sizes for some cancers, yet our study was larger than previous studies. Our study design prevented us from assessing disease severity and whether this may impact offspring cancer.

In conclusion, our population-based nationwide study found an increased association of childhood cancers in the offspring of mothers with autoimmune diseases. It was not possible to evaluate any increased cancer association in this study from medication use. However, treating mothers with autoimmune diseases may improve pregnancy and birth outcomes.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejcped.2024.100145.

References

[1] X. Huang, J. Hansen, P.-C. Lee, C.-K. Wu, N. Federman, O.A. Arah, et al., Maternal diabetes and childhood cancer risks in offspring: two population-based studies, Br. J. Cancer (2022) 1–6.
[2] H. Zierhut, M.S. Linet, L.L. Robison, R.K. Severson, L. Spector, Family history of cancer and non-malignant diseases and risk of childhood acute lymphoblastic leukemia: a Children's Oncology Group Study, Cancer Epidemiol. 36 (2012) 45–51.
[3] M.L. Kwan, C. Metayer, V. Crouse, P.A. Buffler, Maternal illness and drug/medication use during the period surrounding pregnancy and risk of childhood leukemia among offspring, Am. J. Epidemiol. 165 (2007) 27–35.
[4] H.T. Orimoloye, J.E. Heck, A. Charles, C. Saechao, D. He, N. Federman, et al., Maternal migraine and risk of pediatric cancers, Pediatr. Blood Cancer (2023) e30385.
[5] F. Angum, T. Khan, J. Kaler, L. Siddiqui, A. Hussain, The prevalence of autoimmune disorders in women: a narrative review, Cureus 12 (2020).
[6] É. Vinet, S. Bernatsky, Outcomes in children born to women with rheumatic diseases, Rheum. Dis. Clin. 43 (2017) 263–273.

[7] H.-C. Lin, S.-F. Chen, H.-C. Lin, Y.-H. Chen, Increased risk of adverse pregnancy outcomes in women with rheumatoid arthritis: a nationwide population-based study, Ann. Rheum. Dis. 69 (2010) 715–717.
[8] E.L. Marcotte, T.P. Thomopoulos, C. Infante-Rivard, J. Clavel, E.T. Petridou, J. Schüz, et al., Caesarean delivery and risk of childhood leukaemia: a pooled analysis from the Childhood Leukemia International Consortium (CLIC), Lancet Haematol. 3 (2016) e176–e185.
[9] S. Sitia, F. Atzeni, P. Sarzi-Puttini, V. Di Bello, L. Tomasoni, L. Delfino, et al., Cardiovascular involvement in systemic autoimmune diseases, Autoimmun. Rev. 8 (2009) 281–286.
[10] J. Buckley, G. Gilchrist, K. Ruccione, H. Sather, W. Woods, G. Hammond, Multiple sclerosis in mothers of children with acute lymphoblastic leukemia, Leukemia 3 (1989) 736–739.
[11] L. Mellemkjaer, F. Alexander, J. Olsen, Cancer among children of parents with autoimmune diseases, Br. J. Cancer 82 (7) (2000) 1353.
[12] F. Perillat-Menegaux, J. Clavel, M.-F. Auclerc, A. Baruchel, G. Leverger, B. Nelken, et al., Family history of autoimmune thyroid disease and childhood acute leukemia, Cancer Epidemiol. Biomark. Prev. 12 (2003) 60–63.
[13] W.-Q. Wen, X.-O. Shu, T. Sellers, S. Bhatia, B. Lampkin, L.L. Robison, Family history of cancer and autoimmune disease and risk of leukemia in infancy: a report from the Children's Cancer Group (United States and Canada), Cancer Causes Control. 9 (1998) 161–171.
[14] M. Till, N. Rapson, P. Smith, Family studies in acute leukaemia in childhood: a possible association with autoimmune disease, Br. J. Cancer 40 (1979) 62–71.
[15] K. Ekstrom, H. Hjalgrim, L. Brandt, E. Baecklund, L. Klareskog, A. Ekbom, et al., Risk of malignant lymphomas in patients with rheumatoid arthritis and in their first-degree relatives, Arthritis Rheum. 48 (2003) 963–970.
[16] L. Mellemkjér, V. Andersen, M.S. Linet, G. Gridley, R. Hoover, J.H. Olsen, Non-Hodgkin's lymphoma and other cancers among a cohort of patients with systemic lupus erythematosus, Arthritis Rheum. 40 (1997) 761–768.
[17] L.K. Seppälä, L.M. Madanat-Harjuoja, R. Troisi, J.N. Sampson, M.K. Leinonen, K. Vettenranta, Maternal autoimmune disease is not associated with cancer in the offspring, Acta Paediatr. 110 (2021) 2259–2266.
[18] M.L. Gjerstorff, The Danish Cancer Registry, Scand. J. Public Health 39 (2011) 42–45.
[19] E. Steliarova-Foucher, M. Colombet, L.A.G. Ries, F. Moreno, A. Dolya, F. Bray, et al., International incidence of childhood cancer, 2001–10: a population-based registry study, Lancet Oncol. 18 (2017) 719–731.
[20] C.B. Pedersen, The Danish Civil Registration System, Scand. J. Public Health 39 (2011) 22–25.
[21] M. Bliddal, A. Broe, A. Pottegård, J. Olsen, J. Langhoff-Roos, The Danish Medical Birth Register, Eur. J. Epidemiol. 33 (2018) 27–36.
[22] K.D. Deane, J.M. Norris, V.M. Holers, Preclinical rheumatoid arthritis: identification, evaluation, and future directions for investigation, Rheum. Dis. Clin. North Am. 36 (2010) 213–241.
[23] W.W. Eaton, M.G. Pedersen, H.O. Atladottir, P.E. Gregory, N.R. Rose, P. B. Mortensen, The prevalence of 30 ICD-10 autoimmune diseases in Denmark, Immunol. Res 47 (2010) 228–231.
[24] I. Behrens, S. Basit, J.A. Lykke, M.F. Ranthe, J. Wohlfahrt, H. Bundgaard, et al., Association between hypertensive disorders of pregnancy and later risk of cardiomyopathy, JAMA 315 (2016) 1026–1033.
[25] S. Greenland, Modeling and variable selection in epidemiologic analysis, Am. J. Public Health 79 (1989) 340–349.
[26] H.Ó. Atladóttir, P. Thorsen, L. Østergaard, D.E. Schendel, S. Lemcke, M. Abdallah, et al., Maternal infection requiring hospitalization during pregnancy and autism spectrum disorders, J. Autism Dev. Disord. 40 (2010) 1423–1430.
[27] L. Din, M. Sheikh, N. Kosaraju, K.E. Smedby, S. Bernatsky, S.I. Berndt, et al., Genetic overlap between autoimmune diseases and non-Hodgkin lymphoma subtypes, Genet Epidemiol. 43 (2019) 844–863.
[28] S. Tsuda, A. Sameshima, M. Sekine, H. Kawaguchi, D. Fujita, S. Makino, et al., Pre-conception status, obstetric outcome and use of medications during pregnancy of systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and inflammatory bowel disease (IBD) in Japan: multi-center retrospective descriptive study, Mod. Rheumatol. 30 (2020) 852–861.
[29] A. Doria, P. Sarzi-Puttini, Y. Shoenfeld, Infections, rheumatism and autoimmunity: the conflicting relationship between humans and their environment, Autoimmun. Rev. 8 (2008) 1–4.
[30] M. Smith, Considerations on a possible viral etiology for B-precursor acute lymphoblastic leukemia of childhood, J. Immunother. 20 (1997) 89–100.
[31] G. Stafford, N. Villén, A. Roso-Llorach, A. Troncoso-Mariño, M. Monteagudo, C. Violán, Combined multimorbidity and polypharmacy patterns in the elderly: a cross-sectional study in primary health care, Int. J. Env. Res. Public Health 18 (2021) 9216.
[32] J. Schüz, T. Weihkopf, P. Kaatsch, Medication use during pregnancy and the risk of childhood cancer in the offspring, Eur. J. Pedia 166 (2007) 433–441.
[33] H. Ince-Askan, P.R. Mandaviya, J.F. Felix, L. Duijts, J.B. van Meurs, J.M. Hazes, et al., Altered DNA methylation in children born to mothers with rheumatoid arthritis during pregnancy, Ann. Rheum. Dis. 78 (2019) 1198–1204.
[34] L.R. Jølving, J. Nielsen, U.S. Kesmodel, R.G. Nielsen, S.S. Beck-Nielsen, B. M. Nørgård, Children born by women with rheumatoid arthritis and increased susceptibility for chronic diseases: a nationwide cohort study, Arthritis Care Res 70 (2018) 1192–1197.
[35] A. Illes, L. Varoczy, G. Papp, P. Wilson, P. Alex, R. Jonsson, et al., Aspects of B-Cell non-hodgkin's lymphoma development: a transition from immune-reactivity to malignancy, Scand. J. Immunol. 69 (2009) 387–400.
[36] S. Yadlapati, P. Efthimiou, Autoimmune/inflammatory arthritis associated lymphomas: who is at risk? BioMed. Res Int (2016) 8631061.
[37] K.Y. Urayama, P.D. Thompson, M. Taylor, E.A. Trachtenberg, A.P. Chokkalingam, Genetic variation in the extended major histocompatibility complex and susceptibility to childhood acute lymphoblastic leukemia: a review of the evidence, Front. Oncol. 3 (2013) 300.
[38] J.F. Fries, F. Wolfe, R. Apple, H. Erlich, T. Bugawan, T. Holmes, et al., HLA–DRB1 genotype associations in 793 white patients from a rheumatoid arthritis inception cohort: frequency, severity, and treatment bias, Arthritis Rheum. 46 (2002) 2320–2329.
[39] K.W. Wucherpfennig, HLA and Autoimmunity. Immunogenetics of Autoimmune Disease, Springer, 2006, pp. 1–12.
[40] M. Schmidt, S.A.J. Schmidt, J.L. Sandegaard, V. Ehrenstein, L. Pedersen, H. T. Sørensen, The Danish National Patient Registry: a review of content, data quality, and research potential, Clin. Epidemiol. 7 (2015) 449.
[41] M. Pedersen, M. Klarlund, S. Jacobsen, A.J. Svendsen, M. Frisch, Validity of rheumatoid arthritis diagnoses in the Danish National Patient Registry, Eur. J. Epidemiol. 19 (2004) 1097–1103.