Maternal Diabetes and Risk of Childhood Cancer in the Offspring

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Novelty and impact

This is a nationwide, population-based registry study with detailed data on exposure. Our results support an association between maternal diabetes and childhood cancer in the offspring. We found the risk of cancer among the offspring to be elevated, especially for those born to mothers with gestational diabetes and highest for leukemias and some solid tumors. As a novel finding, our study suggests a trend towards a risk-reducing impact of maternal diabetes medication.

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Abbreviations:

AGA= Appropriate for gestational age

CI= Confidence interval

CNS= Central nervous system

DM = Diabetes mellitus

FCR= Finnish Cancer Registry

HILMO= Care Registry for Health Care

IGF-1= Insulin-like Growth Factor 1

Kela= Social Insurance Institute of Finland

LGA= Large for gestational age

MBR= Medical Birth Registry

OR= Odds ratio

SGA= Small for gestational age

THL= National Institute for Health and Welfare

Abstract

An association between maternal diabetes, its medication and childhood cancer has not been previously explored in a registry-based setting. With a case-control design, we aimed to explore whether maternal diabetes is associated with an increased risk of childhood cancer in the offspring. Combining data from population-based registries, we analyzed a total of 2,029 cases, i.e. persons with childhood cancer diagnosed under the age of 20 years between years 1996-2014 and a total of 10,103 matched population controls. The mothers of the cases/controls and their diagnoses of diabetes (DM) before/during pregnancy as well as their insulin/metformin prescriptions during pregnancy were identified. Conditional logistic regression modelling was used to analyze the risk of childhood cancer. The OR for childhood cancer among those exposed to any maternal diabetes was 1.32 (95% CI 1.14-1.54) compared to the offspring of the non-diabetic mothers. The effect of maternal diabetes on the risk of childhood cancer remained elevated even after adjusting for maternal age, parity and smoking. Our data suggest that maternal diabetes medication may reduce the risk for childhood cancer (adjusted OR 0.83, 95% CI 0.36-1.94), especially in gestational diabetes (adjusted OR 0.26, 95% CI 0.05-1.25), compared to the diabetic mothers without medication. The risk of childhood leukemia was significantly higher among children exposed to any maternal diabetes (OR 1.36, CI 1.04-1.77) compared to the unexposed. Maternal diabetes appears to be associated with an increased risk of childhood cancer in the offspring. The possible risk-reducing effect of an exposure to diabetes medication on offspring cancer risk warrants further investigation.

Introduction

The early onset of childhood cancer implicates etiological involvement of both genetic factors and/or early (pre- and perinatal) environmental exposures. However, to date, evidence suggests only an estimated fraction of 5-10% of childhood cancer to be explained by identified, hereditary cancer syndromes.[1,2] As the bulk of epidemiological data supports a significant causal role for environmental exposures in the risk of a wide range of cancer,[3-6] there is an obvious need to evaluate the role of early exposures in the etiology of childhood cancer.

The risk of adult cancer has been shown to be elevated among patients with type 1 or 2 diabetes.[7,8] For type 2 diabetes, the increased risk is observed regardless of confounding factors,[7,9,10] such as obesity, a widely recognized risk factor for cancer.[11] The potential contributors to the increased risk among diabetics are many, including at least hyperglycemia and -insulinism affecting all tissues, as well as site-specific mechanisms affecting certain organs, i.e. the liver and pancreas, through oxidative stress. These increase the amount of insulin receptors, overexpressed in cancer cells, altering growth, but also potential contributors like IGF-1 receptors, inducing cancer cell growth selectively.[10,12-15] Both endo- and exogenous hyperinsulinism increase the risk of cancer.[12-14,16] There are data suggesting that type 2 diabetes medication, especially metformin, may contribute to a decrease in the risk of cancer in diabetes patients.[17,18]

Maternal type 1, 2 and gestational diabetes all appear to have an association with childhood cancer in the offspring.[19-22] The association between maternal diabetes and childhood cancer is most convincing for acute lymphoblastic leukemia (ALL),[22,23] but with only few studies differentiating pregestational from gestational diabetes.[19,21,23-24] Whether modifiable factors affecting the anthropometrics at birth, such as maternal diabetes and diabetes medication, may impact childhood carcinogenesis, remains to be delineated.

Our aim was, in a population-based registry setting, and using a case-control design, to study whether maternal diabetes and its medication are associated with the risk of childhood and adolescent cancer in the offspring. As an additional exposure, we explored the association of birth weight with childhood cancer risk.

Materials and methods

We used the key Finnish, nationwide registries described below and in *Appendix 1*.A unique personal identity code, given to each Finnish citizen since 1967 allows a linkage of information between the different health registries. The Finnish Cancer Registry (FCR) was founded in 1952 and commenced systematic, nationwide registration of cancer in 1953. The FCR includes data on patients, cancer, treatments and causes of death. The FCR has 95% overall coverage.[25]

The ongoing Drugs and Pregnancy -project (1996 onwards) has compiled data from several national health registers: the Medical Birth Register (MBR), Register on Induced Abortions and that on Congenital Malformations (all maintained by the National Institute for Health and Welfare, THL) as well as the Register on Reimbursed Drug Purchases and that on Medical Special Reimbursements maintained by the Social Insurance Institute of Finland (Kela). This project was designed to evaluate the pattern of drug use during pregnancy and estimate the impact of medication on pregnancy outcomes. The material is cumulatively supplemented on a biannual basis.

The Care Register for Health Care (HILMO) is maintained by THL from the year 1994 onwards. It is a continuation of the preceding Hospital Discharge Register (1969-1993). Currently, HILMO contains data on patients discharged from inpatient care (since 1969), on day surgeries (since 1994) and on hospital outpatient visits in public hospitals (since 1998).

With the study being fully registry -based, no ethical board approval was required. The respective research permits from THL, Kela and Helsinki University Hospital for this study have been obtained.

Study population

All births during the years 1996-2014 were identified through the MBR (*n=1 108 754*). By then linking to the Finnish Cancer Registry we identified our cases, defined as all subjects diagnosed with cancer under the age of 20 years (n=*2,037*). From the MBR, we then identified five birthyear and sex-matched population controls for each case (*n=10,185*). The medical information on the mothers and children was obtained from the HILMO and the MBR. The mothers of the cases and controls, diagnosed with pregestational diabetes prior to pregnancy, or with gestational diabetes during pregnancy, and those with insulin and/or metformin medication during pregnancy, were identified. Due to missing data on birth weight or gestational age of the offspring a total of 8 cases and 82 controls were excluded from the analysis as described in *Figure 1*. The key demographics of the groups are given in *Table 1.*

Exposure definition and classification

The mothers with offspring exposed to pregestational or gestational diabetes were identified with the maternal ICD- codes (versions ICD-9 and ICD-10). With the ICD-10 we used the diabetes codes E10-E14 and O24.0, O24.1, O24.4 and O24.9, and for ICD-9 codes 250, i6480A and i6488A were used. Pregestational diabetes was defined as a diagnosis any time before pregnancy, and gestational diabetes as a diagnosis given between the beginning of pregnancy and delivery. The date of conception was calculated as the date of delivery minus the gestational age at birth in days based on the best clinical estimate (the majority with ultrasound confirmation), and as registered in the MBR. Additional information on possible diabetes exposure of the offspring was gathered from the MBR data on pathological glucose tolerance test(s) during pregnancy and/or the MBR diabetes record, and from the drug reimbursement codes from Kela. The diabetes medication was identified with the ATC-codes A10A for insulin and A10B for metformin. More detailed information on the diabetes classification used is provided in *Appendix 2*.

Information on birth weight was retrieved from the MBR and categorized as children born weighing > or ≤ 4000g. Birth weight was also related to the gestational age and categorized as small (SGA),

appropriate (AGA) or large for gestational age (LGA). SGA was defined as birth weight under -2 SD and LGA over +2 SD of the standard population- based growth-curves.[26]

Outcome definition and classification

The outcome was defined as being diagnosed with first cancer by the age of 20 years. Cancer was defined as a malignant neoplasm, but also including benign or borderline tumors of the central nervous system (CNS). The Finnish Cancer Registry uses both the ICD-0-3 and ICCC3 classification[27] to classify childhood cancers. Malignancies were classified using the ICCC3 code 011 for ALL, 011-015 for all leukemias, 021-025 for lymphomas, 031-036 for CNS tumors and 041-122 for other cancers.

Statistical analysis

Conditional logistic regression modelling was applied to estimate the odds ratios for childhood cancer comparing children of diabetic mothers to those of healthy mothers. The risk of childhood cancer in the offspring was also evaluated separately for pregestational and gestational diabetes as well as type of diabetes medication (insulin/metformin). In addition to the crude odds ratios, we also fitted a model adjusting for maternal age (< 25, 25-29, ≥ 30 years), parity (1^{st},2^{nd}, ≥ 3^{rd}), and smoking (yes/no). Cases/controls with missing data on maternal smoking were omitted from the analysis. The reference maternal age was set at 25-29 years at delivery. For parity we chose the first child to be the reference category. The association between birth weight and risk of childhood cancer was first assessed for data validation. As birth weight is considered a mediator for childhood cancer, it was not included in the analyses. A sensitivity analysis including maternal pre-pregnancy BMI was conducted restricting data to the years 2004-2014 as the MBR began collecting information on maternal weight and height in 2004. Statistical analyses were performed with STATA MP14 (StataCorp LLC). Additional analyses stratifying by cancer subtypes were also performed.

Data Availability

The data that support the findings of this study are available upon request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Results

We found the risk of childhood cancer to be significantly increased among the offspring exposed to any type of maternal diabetes compared to those not exposed (crude OR 1.32, 95% CI 1.14-1.54). The risk remained elevated even after adjusting for age, parity and the smoking status of the mother (adjusted OR 1.28 95% CI 1.10-1.50). After adjustment, the risk was elevated among those exposed to gestational (adjusted OR 1.31, 95% CI 1.11-1.54), but not among those exposed to pregestational diabetes (adjusted OR 1.11, 95% CI 0.73-1.69).

The adjusted odds ratio for childhood cancer in the offspring exposed to maternal diabetes without medication was 1.31 (95%CI 1.11-1.55). The risk estimates for childhood cancer seemed to be lower following exposure to maternal diabetes with metformin medication (crude OR 0.99, 95% CI 0.46-2.15, adjusted OR 1.04,95% CI 0.48-2.27). Metformin was taken by 10 mothers in the case and 50 mothers in the control group. Other associations with diabetes medication compared to non-diabetic mothers were inconclusive. For further results, see *Table 2*. A sensitivity analysis, including an adjusted model with maternal pre-pregnancy BMI, yielded a slightly higher risk (*Appendix 3*).

We also performed an additional analysis comparing the risk for childhood cancer in the offspring, if the diabetic mother was receiving diabetes medication or not. Maternal diabetes medication seemed to lower the risk estimates for childhood cancer (adjusted OR 0.83, 95% CI 0.36-1.94), especially for gestational diabetes (adjusted OR 0.26, 95% CI 0.05-1.25) (*Table 3)*. For the pregestational diabetes the sufficient data was not available due to matched analysis model.

In our analyses by cancer subtype, a possible association between an exposure to any maternal diabetes and childhood leukemia in the offspring was found (crude OR 1.36, 95% CI 1.04-1.77, adjusted OR 1.31, 95% CI 1.00-1.72). The risk for ALL following exposure of maternal pregestational diabetes was twofold compared to the offspring of non-diabetic mothers (adjusted OR 2.10, 95% CI 1.05-4.21) (*Table 4*).

Yet, we did find a significant association (adjusted OR 1.35, CI 1.04-1.77) (Table 4) between the exposure to gestational diabetes and pediatric solid tumors other than CNS (other cancers) with the two largest groups being neuro- and nephroblastomas (20,2% and 15,8%) (data not shown). When adjusting for maternal age, birth order of the child and maternal smoking, the results were not altered. The results by cancer type are presented in *Table 4*.

To cross-validate our data against previously published studies, we also explored the association between birth weight, without information on maternal diabetes, and childhood cancer of the offspring. We found those with a high birth weight (over 4000g) to have an increased risk for childhood ALL (adjusted OR 1.34, 95% CI 1.06-1.69) as well as all leukemias adjusted OR 1.30, 95% CI 1.06-1.60) (data not shown).

Discussion

Our aim was to study maternal diabetes, its medication and their possible impact on the risk of childhood cancer. We found a significant association between fetal exposure to gestational diabetes and the risk of childhood cancer. Our data also demonstrated an elevated risk of childhood leukemia and some solid tumors among the offspring following maternal diabetes exposure.

In a study reporting on data from the California Cancer Registry, an association between several childhood cancer types in the offspring and maternal diabetes and obesity prior to pregnancy was observed. Excessive maternal weight gain during pregnancy also appeared to be a risk factor.[24] A population-based, cohort study in Sweden, showed a 1.6-fold increase in the risk of childhood leukemia by maternal type 1 and gestational diabetes, but with lack of an association between gestational diabetes and central nervous system malignancies (CNS).[22] For other cancers, the results were inconclusive due to a small number of cases. Results from a recent Danish study exploring the influence of maternal diabetes on the risk of childhood ALL found the risk to be increased by at least 2-fold.[23]

Our results support an association between gestational diabetes and childhood cancer in the offspring.[20,21] Furthermore, we re-established the significant association between maternal diabetes and childhood leukemia, in concordance with previous studies.[22,28] In our study the risk for ALL seemed to be increased in offspring exposed to maternal pregestational diabetes. Importantly, and following more accurate exposure definition and classification with multiple information sources, we found the risk for any childhood cancer to be increased especially for gestational diabetes.[23]

Previous studies including data on maternal medication have been hampered by small sample size,[19,23] or have not included the possible impact of medication in the analyses.[20-22,24,28] Despite the small sample size, our data do suggest a possible risk-reducing impact of maternal medication for gestational diabetes on the incidence of childhood cancer in the offspring. This impact was also discernible for any diabetes but especially for gestational diabetes, and was most pronounced when metformin was used, reducing the risk to the population level. Based on our data, further studies on the possibility of a true, protective effect rendered by diabetes medication appear warranted.

Possible biological mechanisms linking maternal diabetes and the emergence of childhood cancer in the offspring are many. First, maternal hyperglycemia is known to affect the epigenetics of the offspring.[29] Second, maternal hyperglycemia, and especially hyperinsulinism, increase the expression of insulin receptors, particularly on cancer cells, as well as the production of IGF-1.[10,12-15] Third, hyperinsulinism can be iatrogenic or endogenous.[12-14,16] These biological mechanisms may lie behind our findings. In gestational diabetes, insulin resistance emerges during pregnancy and increases the amount of insulin and IGF-1 receptors through the impact of hyperglycemia.[30] In pregestational diabetics, the medication has often been initiated years before thus rendering the mother with a more stable glucose homeostasis, at least in early pregnancy, compared to those with gestational diabetes. Yet, medication for gestational diabetes most likely improves maternal glucose homeostasis and thus reduce fetal exposure to hyperglycemia.

The association between birth weight and childhood cancer, especially ALL, has been widely recognized.[31-34] Our results remain in line with those of previous studies and serve to further corroborate the data. A high birth weight and excessive fetal growth are both associated with a higher IGF-1, all known risk factors for childhood cancer, especially ALL.[12,35-38] Birth weight may thus be considered a mediator for the biological impact of maternal diabetes on the risk of cancer in the offspring.

The prevalence of gestational diabetes has been estimated to be around 10-13% in Finland (unpublished data from MBR, shown in the national gestational diabetes guidelines) with that of diabetes reportedly lying at about 11% among women overall.[39] In our data, the prevalence of diabetes was slightly lower, at 9.7%. Most likely our material lacks a group of pregestational and gestational diabetes patients treated in an outpatient setting with dietary counseling only. Another pitfall is that neither do we have information on glucose homeostasis before and during pregnancy nor on the dose-specific drug exposure. These may differ in pregestational and gestational diabetes and thus our results by type of diabetes are to be viewed with some caution. Also, a possibility of misclassification bias or underestimation of the number of diabetes patients with the transfer from the ICD-9 to ICD-10 exists.

Our nationwide and population-based study combines an exceedingly comprehensive set of information on maternal morbidity, perinatal history and cancers among the offspring before the child´s 20th birthday. In the setting of maternal diabetes and the risk for cancer at an early age, our study is the first to suggest a possible, risk-reducing effect posed by the medication shedding additional light on the background of a putative, biological association between the two.[20-23]

Conclusion

Our comprehensive, nationwide, registry-based data, free of recall and selection bias, is strongly indicative of a link between maternal diabetes and the risk of childhood cancer in the offspring, especially that of leukemia and some solid tumors, for which the underlying biological mechanisms

remain to be delineated. A possible, risk-reducing impact rendered by the pharmacotherapy of maternal diabetes on the risk of childhood cancer in the offspring remains to be established.

Conflicts of interest

None of the writers have conflicts of interest to disclose.

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	Cases n=2,029	Proportion (%) or range	Controls n=10,103	Proportion (%) or range	Missing values: Cases/controls
Maternal characteristics					
Age of the mother (median)	30	15-48	29	14-47	0
First child	847	41.7	4,098	40.6	0/4
Smoking					
Yes	291	14.3	1,447	14.3	0
No	1,680	82.8	8,404	83.2	0
Unknown	58	2.9	252	2.5	0
Diabetes diagnosis*	241	11.9	940	9.3	0
Pregestational diabetes**	29	1.4	128	1.3	0
Gestational diabetes***	212	10.4	812	8	0
Any diabetes medication	33	1.6	154	1.5	0
Diabetes medication: insulin	25	1.2	114	1.1	0
Diabetes medication:	10	0.5	50	0.5	0
Diabetes medication: both	2	0	10	0	0
Offspring characteristics					
Female	937	46.1	4,672	46.2	0
Male	1,092	53.8	5,431	53.8	0
Gestational age, weeks (mean)	39	24-43	39	24-42	0
Birth weight (mean)	3,532	825-5,200	3,521	485-5,750	0
Birth weight ≥4000g	400	19.7	1,870	18.5	0
Birth weight <4000g	1,629	80.3	8,233	81.5	0
Gestational age ≥37 weeks	1,888	93.1	9,566	94.7	0
Gestational age <37 weeks	141	6.9	537	5.3	0
Birth weight by gestational age					
SGA	55	2.7	217	2.1	0
AGA	1,881	92.7	9,587	94.9	0
LGA	93	4.6	299	3	0
Twins	67	3.3	319	3.2	0

*Any diabetes diagnosis gathered from MBR, HILMO or Drugs and pregnancy- database.
**Diagnoses E10-E14, O24.0-24.3, i259, i6480a, medical reimbursement code. ***Diagnoses O24.4, O24.9, i6488A, or pathological glucose tolerance test.

Table 1. Baseline characteristics of cases and controls in years 1996-2014.

	Cases N= 2,029 (%)	Controls N= 10,103 (%)	Crude OR*	95% CI	Adjusted OR**	95% CI
Any maternal diabetes	241(11.9)	940 (9.3)	**1.32**	**1.14-1.54**	**1.28**	**1.10-1.50**
Any diabetes medication	33 (1.6)	154 (1.5)	1.14	0.77-1.67	1.12	0.76-1.67
Insulin only	23(1.1)	104 (1.0)	1.16	0.73-1.85	1.13	0.70-1.82
Metformin only	8 (0.4)	40 (0.4)	0.99	0.46-2.15	1.04	0.48-2.27
Insulin and metformin	2(0.1)	10(0.1)	1.57	0.32-7.80	1.41	0.28-7.02
Diabetes without medication	208 (10.2)	786 (7.8)	**1.35**	**1.15-1.59**	**1.31**	**1.11-1.55**
Gestational diabetes	212(10.4)	812(8.0)	**1.35**	**1.14-1.58**	**1.31**	**1.11-1.54**
Any diabetes medication	12(0.6)	84(0.8)	0.80	0.43-1.50	0.84	0.45-1.58
Pregestational diabetes	29 (1.4)	128 (1.2)	1.14	0.76-1.72	1.11	0.73-1.69
Any diabetes medication	21(1.0)	70(0.7)	1.51	0.92-2.49	1.43	0.86-2.37

*Matched analysis without adjustment. **Matched analysis adjusted by maternal age, parity, smoking status.

Table 2. Odds ratios of childhood cancer of the offspring, stratified by medication, compared to offspring of a non-diabetic mother.

Diabetes type	Cases	Controls	Crude OR*	95%CI	Adjusted OR**	95% CI
Any maternal diabetes	N=241 (%)	N=940 (%)				
Any diabetes medication	33 (13.7)	154 (16.4)	0.61	0.28-1.33	0.83	0.36-1.94
Pregestational diabetes	N=29(%)	N= 128 (%)				
Any diabetes medication	21(72.4)	70(54.7)	-	-	-	-
Gestational diabetes	N=212(%)	N=812(%)				
Any diabetes medication	12(5.7)	84(10.3)	**0.20**	**0.04 – 0.88**	0.26	0.05 – 1.25

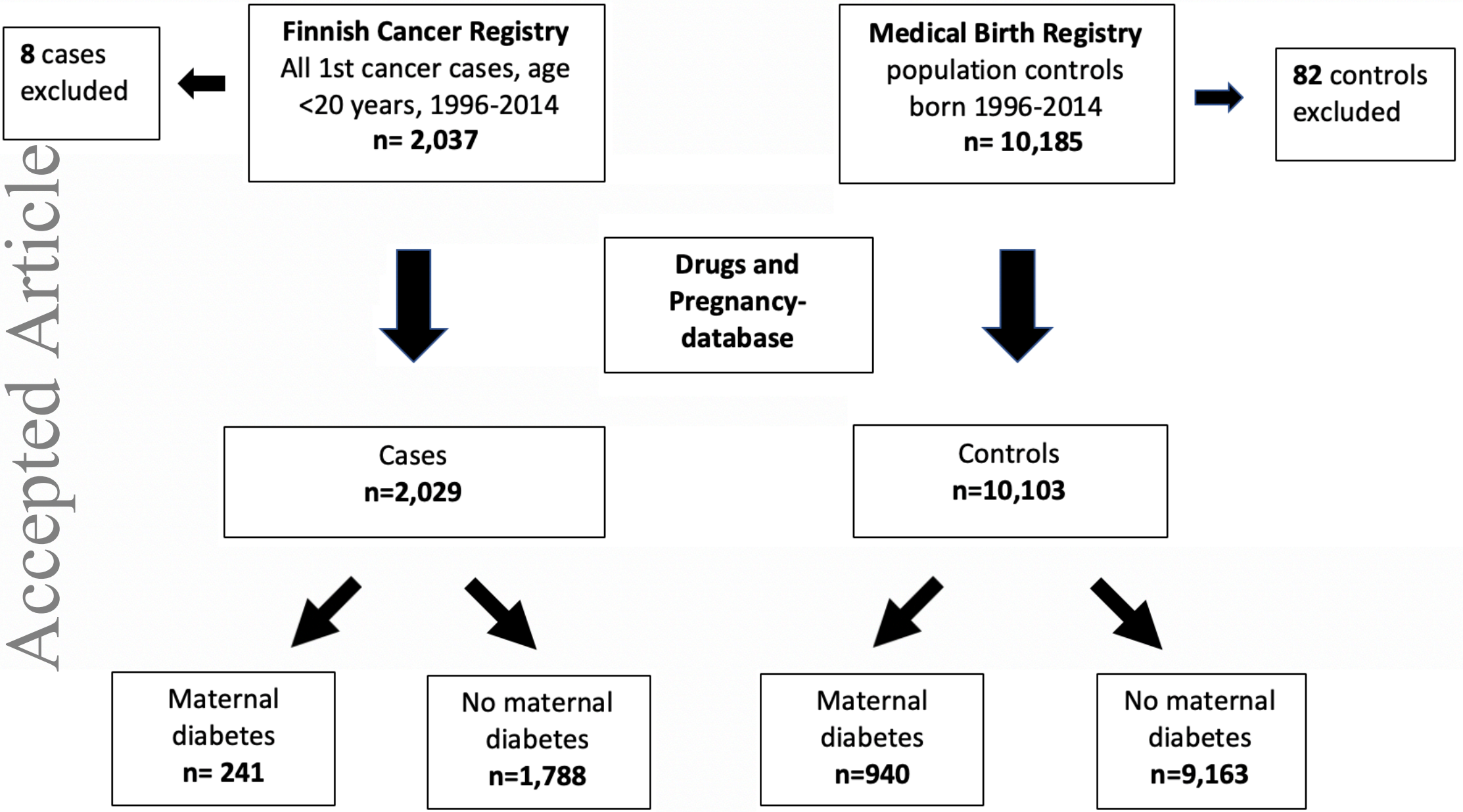
*Matched analysis without adjustment. **Matched analysis adjusted by maternal age, parity, smoking status.
-No sufficient data for matched analysis.

Table 3. Odds ratios of childhood cancer after exposure of maternal diabetes with medication, compared to maternal diabetes with no medication.

Cancer subtypes	Cases N=2,029 (%)	Controls N=10,103 (%)	Crude OR*	95% CI	Adjusted OR**	95% CI
ALL	511 (25.2)	2,544 (25.2)				
Any maternal diabetes	61 (11.9)	247 (9.7)	1.27	0.94-1.72	1.23	0.90-1.68
Pregestational diabetes	12 (2.3)	30 (1.2)	1.97	0.99-3.89	**2.10**	**1.05-4.21**
Gestational diabetes	49 (9.6)	217 (8.8)	1.16	0.83-1.62	1.10	0.78-1.55
All leukemias	649 (32.0)	3,230 (32.0)				
Any maternal diabetes	80 (12.3)	306 (9.5)	**1.36**	**1.04-1.77**	1.31	1.00-1.72
Pregestational diabetes	12 (1.8)	40 (1.2)	1.49	0.77-2.87	1.56	0.80-3.04
Gestational diabetes	68 (10.5)	266 (8.2)	1.33	1.00-1.77	1.26	0.94-1.70
Lymphomas	149 (7.3)	740 (7.3)				
Any maternal diabetes	14 (9.4)	49 (6.6)	1.47	0.78-2.78	1.29	0.66-2.50
Pregestational diabetes	0 (0)	10 (1.4)	_	_	_	_
Gestational diabetes	14 (9.4)	39 (5.3)	1.80	0.95-3.41	1.59	0.81-3.12
CNS	484 (23.9)	2,407 (23.8)				
Any maternal diabetes	56 (11.6)	230 (9.6)	1.24	0.91-1.70	1.23	0.89-1.69
Pregestational diabetes	8 (1.7)	27 (1.1)	1.47	0.66-3.28	1.37	0.61-3.06
Gestational diabetes	48 (9.9)	203 (8.4)	1.19	0.86-1.67	1.19	0.85-1.68
Other cancers	743 (36.6)	3,706 (36.7)				
Any maternal diabetes	89 (12.0)	355 (9.6)	1.29	1.00-1.66	1.27	0.98-1.64
Pregestational diabetes	9 (1.2)	51 (1.4)	0.93	0.45-1.91	0.84	0.39-1.80
Gestational diabetes	80 (10.8)	304 (8.2)	**1.36**	**1.05-1.78**	**1.35**	**1.04-1.77**

*Matched analysis without adjustment **Matched data adjusted by maternal age(categorized), parity, smoking status.
-No sufficient data for matched analysis.

Table 4. Odds ratios for childhood cancer in the offspring, stratified by the cancer subtype.



Picture 1. Flow chart of data formation.

Novelty & Impact Statement:

Only a small fraction of early-onset childhood cancers are linked to hereditary factors, suggesting that environmental exposures, particularly in the mother, significantly impact childhood cancer risk. A potentially important, though understudied environmental factor is maternal diabetes. This investigation of nationwide population-based registry data shows that maternal diabetes is associated with an elevated risk of childhood cancer in offspring. Offspring born to mothers diagnosed with gestational diabetes were at increased risk of childhood leukemia and certain solid tumors in particular. Further investigation is needed to determine whether diabetes medications taken during pregnancy can reduce cancer risk in offspring.