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Maternal diabetes and risk of childhood acute lymphoblastic leukaemia in the offspring

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Background: Maternal diabetes may be linked to childhood acute lymphoblastic leukaemia (ALL) in the offspring.

Methods: We assessed the association between maternal pregestational or gestational diabetes and offspring risk of childhood ALL in a register-based study, including all singletons born in Denmark during 1996–2015 ($n = 1\,187\,482$).

Results: Adjusted hazard ratios of childhood ALL were 2.91 (95% confidence interval (CI): 1.30–6.51) for maternal pregestational diabetes and 1.75 (95% CI: 1.02–2.98) for maternal gestational diabetes. Paternal diabetes did not alter offspring ALL risk, and we found no association between offspring ALL and later maternal risk of diabetes.

Conclusions: Regardless that absolute ALL risk among offspring of women with diabetes remains low, our findings suggest that characteristics of the diabetic intrauterine environment promote ALL development. This offers a setting for future research into the biological mechanisms underlying childhood ALL.

Acute lymphoblastic leukaemia (ALL) is the commonest childhood cancer, with an annual incidence of approximately 4 in 100 000 person-years among children below 15 years of age in developed countries (Hjalgrim *et al*, 2003a; Stiller *et al*, 2006). Apart from certain genetic syndromes, accounting for less than 5% of cases (Stieglitz and Loh, 2013) and a well-established association with high birth weight (Hjalgrim *et al*, 2003b; Caughey and Michels, 2009), risk factors for childhood ALL remain largely unknown. The prenatal origin of most childhood ALL cases has been irrefutably demonstrated by the presence of clone-specific mutations in patient neonatal blood spots (Wiemels *et al*, 1999; Hjalgrim *et al*, 2002; Gruhn *et al*, 2008). While the intrauterine development of preleukaemic cell clones remains unexplained, the association between birth weight and childhood ALL risk suggests that it is related to foetal growth. In addition, a recent study reported an increased ALL risk in children born to women with diabetes (Contreras *et al*, 2016), whose offspring are at increased risk of macrosomia (Schmidt *et al*, 2001; Crowther *et al*, 2005; Temple *et al*, 2006). However, it is unclear whether this association varies by type of maternal diabetes and between ALL subtypes, which may have distinct aetiologies.

We therefore evaluated the risk of ALL among offspring of women with pregestational or gestational diabetes in a cohort study, including all singletons born in Denmark during 1996–2015 identified using nationwide registers with detailed information on maternal antidiabetic medication and ALL subtypes.

MATERIALS AND METHODS

Based on the unique personal identifiers of the children and their parents, we linked information on birth characteristics obtained from the Danish Medical Birth Register (Knudsen and Olsen, 1998) with information on maternal diabetes recorded in the Danish National Patient Register (NPR) (Lynge *et al*, 2011). The NPR contains records of all hospitalisations since 1977, including outpatient contacts since 1995 with diagnoses classified according to the International Classification of Diseases (ICD) 8th (1977–

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Table 1. Person-years of follow-up and number of cases of childhood acute lymphoblastic leukaemia (ALL), according to baseline characteristics and parental diabetes among singletons born in Denmark during 1996–2015

	Person-years at risk (%)	ALL *N* (%)	BCP *N* (%)	*ETV6-RUNX1*/HeH *N* (%)	Total cohort *N* (%)
Total	11 196 998 (100)	492 (100)	431 (100)	266 (100)	1 187 482 (100)
Sex					
Boys	5 745 498 (51.3)	262 (53.3)	222 (51.5)	145 (54.5)	609 514 (51.3)
Girls	5 451 500 (48.7)	230 (46.7)	209 (48.5)	121 (45.5)	577 968 (48.7)
Ethnicity					
Danish	9 334 246 (83.4)	423 (86.0)	370 (85.8)	233 (87.6)	966 532 (81.4)
Other	1 862 752 (16.6)	69 (14.0)	61 (14.2)	33 (12.4)	220 950 (18.6)
Birth order					
1	4 863 355 (43.4)	223 (45.3)	196 (45.5)	116 (43.6)	521 866 (44.0)
2	4 184 761 (37.4)	183 (37.2)	162 (37.6)	104 (39.1)	442 240 (37.2)
⩾3	2 148 882 (19.2)	86 (17.5)	73 (16.9)	46 (17.3)	223 376 (18.8)
Maternal smoking					
No	9 292 764 (83.0)	424 (86.2)	374 (86.8)	229 (86.1)	1 003 943 (84.5)
Yes	1 904 234 (17.0)	68 (13.8)	57 (13.2)	37 (13.9)	183 539 (15.5)
Birth weight (g)[a]		3601	3588	3578	3524
Gestational age (weeks)[a]		39.5	39.4	39.3	39.4
Mode of delivery					
Vaginal	9 359 216 (83.6)	400 (81.3)	350 (81.2)	208 (78.2)	974 473 (82.1)
Caesarean section	1 837 782 (16.4)	92 (18.7)	81 (18.8)	58 (21.8)	213 009 (17.9)
Maternal diabetes					
No	10 976 192 (98.0)	472 (95.9)	415 (96.3)	253 (95.1)	1 157 767 (97.5)
Pregestational	46 598 (0.4)	6 (1.3)	5 (1.2)	4 (1.5)	5409 (0.5)
Gestational	174 208 (1.6)	14 (2.8)	11 (2.5)	9 (3.4)	24 306 (2.0)
First-time pregestational diabetes treatment					
Insulin	35 000 (75.1)	5 (83.3)	5 (100)	4 (100)	3857 (71.3)
Age at pregestational diabetes diagnosis					
<30	40 081 (86.0)	6 (100)	5 (100)	4 (100)	4554 (84.2)
⩾30	6517 (14.0)	0 (0)	0 (0)	0 (0)	855 (15.8)
Paternal diabetes[b]					
No	10 963 593 (98.7)	482 (98.6)	423 (98.8)	261 (99.2)	1 165 777 (98.2)
Yes	148 517 (1.3)	7 (1.4)	5 (1.2)	2 (0.8)	21 435 (1.8)

Abbreviations: ALL = acute lymphoblastic leukaemia; BCP = B-cell precursor ALL; *ETV6/RUNX1* = *ETV6/RUNX1*-positive ALL; HeH = high-hyperdiploidy ALL.
[a]Mean.
[b]Paternal diabetes diagnosed at any time before end of follow-up, including 1 187 212 singletons whose fathers were known from the Civil Registration System.

1993) and 10th revision (1994–). Children registered with Down syndrome in the NPR (ICD10 code Q90) were excluded from the cohort (0.08%) due to their increased risk of childhood leukaemia with distinct biology and aetiology (Izraeli *et al*, 2014).

We defined maternal pregestational diabetes as NPR registrations of ICD8 codes 249 or 250, or ICD10 codes E10–E11 or E13–E14 before gestation. Gestational diabetes was defined as any of the listed ICD codes for diabetes registered for the first time during pregnancy including also ICD10 code O24. For women registered with pregestational diabetes, we retrieved additional information on first-time prescriptions for antidiabetic treatment from the Danish Register of Medicinal Product Statistics (established 1995) (Anatomic Therapeutic Chemical classification system codes A10A for insulin and A10B for oral antidiabetic medications).

ALL occurring before age 15 years was identified through linkage with the Nordic Society of Paediatric Haematology and Oncology leukaemia database (Schmiegelow *et al*, 2010).

The children were followed from birth until date of childhood ALL diagnosis, loss to follow-up/emigration, death, age 15 years, or 31 December 2015, whichever occurred first. We used Cox proportional hazards models with age as the underlying time scale to estimate hazard ratios (HRs) for childhood ALL.

Based on the potential of association with both maternal diabetes and childhood ALL, we adjusted for a number of covariates identified in the Danish Medical Birth Register and the Danish Civil Registration System (Pedersen, 2011). These included the potential confounders maternal age at delivery (continuous), ethnicity (Danish or other), birth order (1, 2 or ⩾3), maternal smoking during pregnancy (yes or no) and birth cohort (5-year intervals), and the potential mediators birth weight (100-g intervals), gestational age (1-week intervals) and mode of delivery (caesarean section or vaginal) (Hjalgrim *et al*, 2004; Chang *et al*, 2006; Thomopoulos *et al*, 2015; Contreras *et al*, 2017). Further, we tested the heterogeneity of the association between maternal diabetes and offspring risk of ALL by birth weight using the median as cut-off (<3540 g *vs* ⩾3540 g).

Childhood ALL was grouped as: (1) all types combined; (2) B-cell precursor ALL; (3) and a group comprising the frequent, prenatally initiated karyotypes (*ETV6/RUNX1*-positive and high-hyperdiploidy ALL).

In subsequent analyses we tested whether paternal diabetes was associated with childhood ALL. Also, we assessed the risk of developing diabetes in women with and without offspring with ALL. In this analysis, we included women with ⩾1 live births between 1996 and 2015, followed from their first birth after 1995 until diabetes diagnosis (outcome), death, emigration, or 31 December 2015, excluding women with diabetes diagnosed before start of follow-up. History of offspring ALL was included as a time-varying variable (exposed from date of offspring ALL diagnosis) with adjustment for maternal age, parity and year of delivery.

All analyses were conducted using SAS statistical software (9.4, SAS Institute, Inc., Cary, NC, USA) with 95% confidence intervals (CIs) based on Likelihood-ratio tests.

Table 2. Association between maternal diabetes, paternal diabetes and risk of childhood acute lymphoblastic leukaemia (ALL) among singletons born in Denmark during 1996–2015

	ALL		BCP		*ETV6-RUNX1*/HeH	
	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Maternal diabetes[a,b]						
No (ref.)	1.00	1.00	1.00	1.00	1.00	1.00
Pregestational	2.92 (1.30–6.53)	2.91 (1.30–6.51)	2.76 (1.14–6.66)	2.75 (1.14–6.65)	3.61 (1.35–9.68)	3.58 (1.33–9.62)
Gestational	1.73 (1.02–2.95)	1.75 (1.02–2.98)	1.54 (0.85–2.80)	1.56 (0.85–2.84)	2.04 (1.05–3.97)	2.06 (1.05–4.03)
Paternal diabetes[c]						
No (ref.)	1.00	1.00	1.00	1.00	1.00	1.00
Yes	1.23 (0.58–2.59)	1.20 (0.57–2.53)	1.01 (0.42–2.45)	0.99 (0.41–2.39)	0.68 (0.17–2.71)	0.66 (0.16–2.65)

Abbreviations: ALL = acute lymphoblastic leukaemia; BCP = B-cell precursor ALL; CI = confidence interval; *ETV6/RUNX1* = *ETV6/RUNX1*-positive ALL; HeH = high-hyperdiploidy ALL; HR = hazard ratio. Crude HRs were implicitly adjusted for age (underlying time scale).
[a]HRs were adjusted for maternal age at delivery (linearly), ethnicity (Danish or other), birth order (1, 2, or ⩾3), maternal smoking (yes or no), and birth cohort (5-year intervals).
[b]The cumulative incidence of ALL before age 15 years was 0.15% (95% CI: 0.06–0.33) among children born to women with pregestational diabetes, 0.08% (95% CI: 0.05–0.14) among children born to women with gestational diabetes, and 0.05% (95% CI: 0.05–0.06) among children born to nondiabetic women (calculations based on Kaplan–Meier estimators).
[c]Paternal diabetes diagnosed at any time before end of follow-up, including 1 187 212 singletons whose fathers were known from the Civil Registration System. HRs were adjusted for paternal age at delivery (linearly), ethnicity (Danish or other), birth order (1, 2, or ⩾3) (same mother), and birth cohort (5-year intervals).

RESULTS

Among 1 187 482 studied singletons, 492 developed ALL before age 15 years (Table 1), corresponding to an annual incidence rate of 4.40 (95% CI: 4.02–4.80) per 100 000 person-years. In total, 5409 children were born to women with pregestational diabetes (mean birth weight: 3519 g) of whom six developed ALL (mean birth weight: 3894 g; mean age at diagnosis: 4.2 years, age range 2–8 years). All mothers to these six children with ALL were diagnosed with diabetes before age 30 years and five mothers had received insulin as first-time antidiabetic treatment. Further, we identified 24 306 children born to women with gestational diabetes (mean birth weight: 3537 g) of whom 14 developed ALL (mean birth weight: 3707 g; mean age at diagnosis: 3.4 years, age range 1–7 years).

After adjusting for potential confounders, childhood ALL risk among children born to women with pregestational or gestational diabetes was 2.91-fold (95% CI: 1.30–6.51) and 1.75-fold (95% CI: 1.02–2.98) increased, respectively, compared with children born to nondiabetic women (Table 2). In analysis of pregestational diabetes, HR were statistically significantly increased for B-cell precursor ALL and for the prenatally initiated karyotypes (*ETV6-RUNX1* or high-hyperdiploidy ALL), while HRs associated with gestational diabetes were only statistically significantly increased among the prenatally initiated karyotypes. The risk estimates remained unchanged in models including only potential confounders (Table 2) and both potential confounders and mediators, respectively (data not shown).

HRs for ALL associated with gestational diabetes did not differ in strata of birth weight (birth weight <3540 g: HR = 1.68, 95% CI: 0.75–3.81 *vs* birth weight $\geqslant 3540$ g: HR = 1.78, 95% CI: 0.88–3.61; p for interaction = 0.92). Neither did we find statistically significant differences between the HRs for ALL associated with pregestational diabetes stratified by birth weight (birth weight <3540 g: HR = 1.10, 95% CI: 0.16–7.87 *vs* birth weight $\geqslant 3540$ g: HR = 4.30, 95% CI: 1.77–10.43; p for interaction = 0.16).

Paternal diabetes was not statistically significantly associated with childhood ALL risk (HR = 1.20, 95% CI: 0.57–2.53) (Table 2). Finally, we found no association between offspring ALL and later risk of diabetes in the mother (HR = 0.92, 95% CI: 0.46–1.85, based on eight mothers diagnosed with diabetes after offspring ALL).

DISCUSSION

In this nationwide register-based cohort study, we found that the risk of childhood ALL in children born to women with pregestational or gestational diabetes was 2.9- and 1.7-fold increased, respectively.

The observed association with pregestational diabetes in our study is likely attributable to type 1 diabetes because the vast majority of these women had received insulin as first-time antidiabetic treatment and were diagnosed before age 30 years. However, the fact that gestational diabetes was also associated with offspring ALL risk suggests that the association with maternal diabetes is not exclusively related to the autoimmunity of type 1 diabetes.

Because of its level of detail regarding both maternal diabetes and offspring ALL, our investigation expands the existing literature on the association between the two conditions considerably. Recently, a statistically significantly 1.4-fold increased ALL risk in offspring of women with pregestational diabetes and a statistically non-significantly 1.3-fold increased ALL risk in offspring of women with gestational diabetes were observed in a California birth record study (Contreras *et al*, 2016). However, unlike in our investigation, information was available on neither type of pregestational diabetes nor on ALL subtypes in the California study. Limitations of similar nature concerning exposure and outcome combined with small study populations have hampered the interpretation of other previous investigations reporting statistically non-significantly increased risks of ALL (McLaughlin *et al*, 2006; Milne *et al*, 2007) or of leukaemia (Petridou *et al*, 1997; Podvin *et al*, 2006) or statistically significantly increased risks of cancer overall (Westbom *et al*, 2002; Wu *et al*, 2012) in offspring of women with diabetes.

Not mirrored by similarly strong associations with paternal diabetes or later maternal diabetes, the increased ALL risk in children born to women with diabetes is unlikely to reflect shared genetic risk factors; rather it may reflect that circumstances characteristic of diabetic pregnancies such as intrauterine hyperglycaemia promote offspring ALL development. In support hereof, we observed that children born to women with pregestational diabetes who developed ALL weighed on average 400 g more than those who did not, suggesting that maternal hyperglycaemia was more pronounced in the former. Birth weight is positively associated with the level of insulin-like growth factor I, which could increase childhood ALL risk by causing proliferation of progenitor or preleukaemic cells (Ross *et al*, 1996). Moreover, maternal hyperglycaemia has been associated with a number of epigenetic modifications in the offspring (Ma *et al*, 2015), which potentially mediate the link between maternal diabetes and offspring's development of ALL.

Although we observed markedly increased relative risks, the cumulative incidence of childhood ALL in offspring of women with diabetes remains low, that is, 0.15 and 0.08% among children

below 15 years of age born to women with pregestational and gestational diabetes, respectively.

The strengths of this study include its nationwide coverage, longitudinal and independent ascertainment of maternal diabetes and offspring ALL development as well as information on important covariates including birth weight. Contrary to previous investigations, our study included information on pregestational diabetes treatment and detailed information on ALL subtypes. Conversely, the low number of children with ALL born to women with pregestational or gestational diabetes had implications for the precision of risk estimates, reflected by the wide CIs. Finally, the apparent absence of association with paternal diabetes or later maternal diabetes was based on a small number of exposed events.

In conclusion, we found that maternal pregestational and gestational diabetes are risk factors for childhood ALL in the offspring. Further studies are needed to identify the biological mechanisms underlying this association.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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