Maternal pregestational or gestational diabetes and childhood wheezing: A population-based cohort study

To the editor

Early-life exposures that modify intrauterine environment may influence the development of wheezing and asthma in children. Diabetes may be one of these compromising factors, possibly through mechanisms related to alterations in fetal allergen sensitization and lung maturation disruption (1, 2). Previous studies on diabetes and offspring wheezing/asthma have revealed contradicting findings (3, 4). Until now, no studies have examined whether the association between maternal diabetes and childhood wheezing/asthma varies by both types of diabetes and wheezing/asthma phenotypes.

Methods

We conducted a register-based cohort study, utilizing data from all Danish residents. We identified 569,649 liveborn singletons during 1996–2004 from the Danish Medical Birth Registry. We excluded 3,954 children with missing or gestational age < 22 weeks or > 45 weeks, 18,244 children who emigrated and 2,774 children who died before their 6th birthday.

We retrieved information on diabetes diagnoses from the Danish National Diabetes Register, which contains information on patients with diabetes treated in either primary or hospital care in Denmark. We additionally identified mothers with gestational diabetes (ICD-10 code O24.4) in the Danish National Patient Register (DNPR). Type of diabetes was categorized as pregestational or gestational diabetes according to the timing of first treatment. We further classified pregestational diabetes into type 1 or type 2 diabetes (Supplemental Figure S1):

1) According to the DNPR diagnosis if the mother had one type of diabetes diagnosis recorded.
2) For those first diagnosed after 1995 and with no record in the DNPR, or those with both type 1 and type 2 diabetes records: according to first-time antidiabetic prescription, insulin for type 1 diabetes, and oral antidiabetics for type 2 diabetes.
3) For those remaining, with undetermined diabetes type, we used age at first-time diabetes treatment < 30 and ≥30 years as the cut-off for type 1 and type 2 diabetes respectively (5).

Our outcomes of interest were childhood wheezing phenotypes determined by wheezing treatment (i.e., hospital treatment for wheezing or anti-asthmatic drug treatment) during 0–3 years of age and 4–6 years similar to a previous study from our group (6). Information on hospital treatment was based on ICD-10 codes J45 and J46 from the DNPR and anti-asthmatic drug treatment based on Anatomical Therapeutical Chemical classification codes (Supplemental Table S1) from the Danish National Prescription Registry. We defined wheezing treatment at age 0–3 years as at least two anti-asthmatic drug prescriptions within one year period or at least one hospital treatment for wheezing during 0–3 years. Wheezing treatment at age 4–6 years was similarly defined. We categorized children into four mutually exclusive groups:
1) *No wheezing:* no wheezing treatment;
2) *Early-onset transient wheezing:* wheezing treatment during 0–3 years of age only;
3) *Early-onset persistent wheezing*: wheezing treatment both during 0–3 years and 4–6 years of age;
4) *Late-onset wheezing*: wheezing treatment during 4–6 years of age only.

Note that for the present study we termed our outcome of interest as wheezing and not asthma, acknowledging the challenges in diagnosing symptoms related to narrowing of airways and breathing problems in young children.

Statistical analyses were performed with Stata 15.0. Since odds ratios tend to overestimate associations when outcomes are common, we used log-binomial regression to analyze the data with robust standard errors, as some individuals are siblings. The magnitude of the associations of each type of maternal diabetes with each wheezing phenotype was presented as prevalence ratios (PRs). The following confounders were included: maternal age, parity, smoking during pregnancy, asthma, thyroid disorders before childbirth, employment status at conception, and child calendar year at birth. Values for covariates were missing for 3.8% of children, and we applied 20 imputations to impute missing values.

Results

Of 544,677 children, 3,146 (0.6%) were born to mothers with pregestational type 1 diabetes, 841 (0.2%) with pregestational type 2 diabetes, and 7,913 (1.5%) with gestational diabetes. Table 1 shows the characteristics of the study subjects.

Gestational diabetes was associated with small increased risk of early-onset transient wheezing (adjusted PR=1.08, 95% CI: 1.00–1.17) and early-onset persistent wheezing (PR=1.15, 95% CI: 1.05–1.26) in offspring, compared to mothers without diabetes. Pregestational type 1 diabetes was associated with a clearly increased risk of early-onset wheezing in offspring: PRs were 1.30 (95% CI: 1.17–1.45) for early-onset transient wheezing and 1.25 (95% CI: 1.08–1.44) for early-onset persistent wheezing. Neither gestational nor type 1 diabetes was associated with offspring late-onset wheezing. We found no

evidence that pregestational type 2 diabetes was associated with any wheezing phenotypes in children (Figure 1).

Altogether 9.4% of the 11,900 children were born to mothers with diabetes complications (ketoacidosis or diabetic coma, nephropathy, retinopathy, neuropathy, or vasculopathy/angiopathy) before childbirth; these children had higher risk of early-onset transient (PR=1.22, 95% CI: 0.97– 1.52) and persistent wheezing (PR=1.21, 95% CI: 0.91–1.61) than children of mothers without diabetes (Supplemental Table S2).

The results were similar when we repeated our analyses among those with one recorded type of diabetes (Supplemental Table S3). The associations of offspring wheezing phenotypes with type 1 diabetes remained unchanged after further adjustment for maternal prepregnancy body mass index, while the associations with gestational diabetes were no longer statistically significant (Supplemental Figure S2).

Discussion

Pregestational type 1 and gestational diabetes were associated with small increased risk of early-onset transient wheezing and persistent wheezing, but not late-onset wheezing in offspring. Pregestational type 2 diabetes was not associated with any childhood wheezing phenotypes.

Currently, the underlying mechanisms behind the association between maternal diabetes and childhood wheezing are unknown. In the presence of diabetes, the fetus is exposed to abnormally high glucose levels, whereas the fetal pancreas exhibits limited responses to acute changes in cord blood glucose (7).

This may result in fetal hyperinsulinemia and consequently hypoxia (2), leading to lung maturation disruption (8). If this is true, we also would expect to see an impact of pregestational type 2 diabetes, which was not observed. It is possible that mothers with type 2 diabetes have better glycemic control than mothers with type 1 or gestational diabetes (9). Our finding of particularly increased risk in mothers with diabetes complications may implicate poor glycemic control. Additionally, type 1 diabetes is an autoimmune disease, and autoantibodies that cross the placenta may act directly on fetal lung development (10). Further research and replications are needed to validate our findings and determine the likely complex mechanisms underlying diabetes and risk of offspring wheezing.

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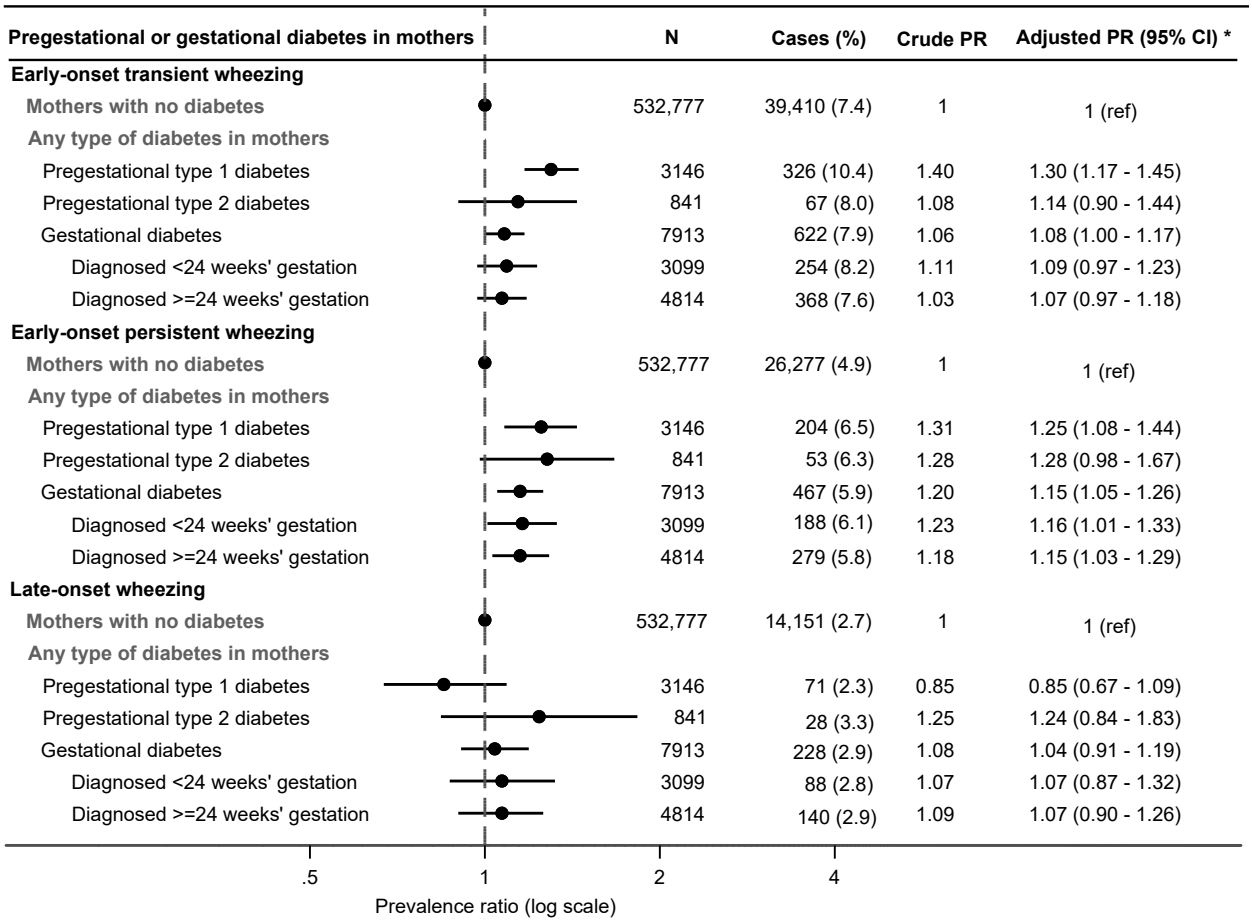
Table 1. Characteristics of study population

Characteristics	Mothers without diabetes (n=532,777)	Mothers with diabetes		
		Pregestational Type 1 diabetes (n=3,146)	Pregestational Type 2 diabetes (n=841)	Gestational diabetes (n=7,913)
Maternal age at delivery (years)				
<25	80,456 (15.1)	343 (10.9)	23 (2.7)	795 (10.1)
25–29	194,368 (36.5)	1,205 (38.3)	66 (7.8)	2,306 (29.1)
30–34	180,595 (33.9)	1,210 (38.5)	291 (34.6)	2,779 (35.1)
≥35	77,358 (14.5)	388 (12.3)	461 (54.8)	2,033 (25.7)
Parity				
1	229,948 (43.2)	872 (27.7)	112 (13.3)	3,000 (37.9)
≥2	302,829 (56.8)	2,274 (72.3)	729 (86.7)	4,913 (62.1)
Maternal smoking during pregnancy				
Yes	115,440 (21.7)	703 (22.3)	161 (19.1)	1,643 (20.8)
No	397,663 (74.6)	2,201 (70.0)	628 (74.7)	5,835 (73.7)
Missing	19,674 (3.7)	242 (7.7)	52 (6.2)	435 (5.5)
Maternal employment status at conception				
Unskilled workers or not in labor market	191,501 (35.9)	1,275 (40.5)	410 (48.8)	3,280 (41.5)
Skilled workers and white-collar workers	207,950 (39.0)	1,272 (40.4)	257 (30.6)	3,065 (38.7)
Top-level status	133,075 (25.0)	597 (19.0)	174 (20.7)	1,565 (19.8)
Missing	251 (<0.1)	<5	0	<5
Calendar year of birth				
1996–1998	181,684 (34.1)	864 (27.5)	176 (20.9)	2,476 (31.3)
1999–2001	178,377 (33.5)	1,102 (35.0)	304 (36.2)	2,461 (31.1)
2002–2004	172,716 (32.4)	1,180 (37.5)	361 (42.9)	2,976 (37.6)
Maternal diabetes complications before childbirth	-	1,003 (31.9)	85 (10.1)	36 (0.5)
Maternal asthma before childbirth	59,809 (11.2)	482 (15.3)	135 (16.1)	1,178 (14.9)
Maternal thyroid disorders before childbirth	7,133 (1.3)	145 (4.6)	40 (4.8)	172 (2.2)
Preterm birth	24,614 (4.6)	739 (23.5)	106 (12.6)	608 (7.7)
Fetal growth *				
Small for gestational age	52,202 (9.8)	136 (4.3)	46 (5.5)	557 (7.0)
Appropriate for gestational age	428,903 (80.5)	1,886 (60.0)	567 (67.4)	5,664 (71.6)
Large for gestational age	51,672 (9.7)	1,124 (35.7)	228 (27.1)	1,692 (21.4)

Figures are numbers (%). * Small for gestational age is defined as a birth weight below the 10th percentile of birth weight by the gestational age and sex, and large for gestational age as above the 90th percentile. The p-values for the comparison of differences among the four diabetes exposure categories were all less than 0.001, using chi-square tests.

Figure 1. Prevalence ratios of early-onset transient, early-onset persistent, and late-onset wheezing according to type of maternal diabetes diagnosis (N=544,677)



Abbreviations: PR, prevalence ratio; CI, confidence interval.

*Adjusted for maternal age at childbirth (<25, 25–29, 30–34, and ≥35 years), maternal asthma (yes/no), maternal smoking during pregnancy (yes/no), maternal parity at the index pregnancy (1st, or 2nd and above), maternal thyroid disorders before childbirth (ICD-8 codes 240–246 and ICD-10 codes E00–E07; yes/no), maternal employment status at conception (unskilled workers or not in labor market, skilled workers and white-collar workers, and top-level status), and calendar year at birth (1996–1998, 1999–2001, and 2002–2004).