# Academic Achievement in Primary School in Offspring Born to Mothers With Type 1 Diabetes (the EPICOM Study): A Register-Based Prospective Cohort Study

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## OBJECTIVE

**This study examined the effect of maternal pregestational type 1 diabetes on offspring primary school performance.**

## RESEARCH DESIGN AND METHODS

**We performed a prospective combined clinical and register-based cohort study comparing primary school performance in offspring (*n* = 707) of women with pregestational type 1 diabetes with matched control offspring (*n* = 60,341). We also examined the association between $HbA_{1c}$ levels during pregnancy and later school performance among offspring born to women with pregestational type 1 diabetes.**

## RESULTS

**Offspring of mothers with pregestational type 1 diabetes obtained similar school grades as control offspring when finishing primary school (regression coefficient [β] = –0.13; 95% CI = –0.30 to 0.03; *P* = 0.12). Adjusting for parental education also resulted in an insignificant difference between the two groups (β = –0.07; 95% CI = –0.23 to 0.09; *P* = 0.37). Among offspring of women with type 1 diabetes, increasing maternal $HbA_{1c}$ pregestationally and throughout the pregnancy was associated with lower average school grades. Offspring born to mothers with good glycemic control in the third trimester obtained higher average school grades compared with control offspring. The opposite applied to offspring born to mothers with inadequate glycemic control, who obtained significantly lower average school grades compared with control offspring.**

## CONCLUSIONS

**Offspring of mothers with pregestational type 1 diabetes obtained similar average grades when finishing primary school compared with matched control offspring. Among offspring of women with type 1 diabetes, we found a consistent negative association between maternal $HbA_{1c}$ in pregnancy and primary school grades. However, whether this association reflects a direct causal influence of intrauterine hyperglycemia is uncertain.**


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Maternal type 1 diabetes during pregnancy increases offspring risk of stillbirth, perinatal disease, and congenital malformations (1–4). The mechanisms behind these adverse pregnancy outcomes have been debated, and intrauterine hyperglycemia leading to modifications of the fetus has been suggested. Long-term consequences of being born to a mother with pregestational type 1 diabetes include higher risk of developing type 2 diabetes and metabolic syndrome (5–11). Studies have also explored the potentially harmful effect of intrauterine hyperglycemia on the developing fetal central nervous system, but other conditions during fetal life, birth complications, neonatal complications, and socioeconomic factors also contribute to later neurocognitive function. Still, studies are so far few and results are conflicting. Two population-based epidemiological studies in Sweden found indications of impaired cognitive function (12,13). Another Scandinavian study from Denmark found that offspring of women with type 1 diabetes obtained lower global cognitive scores compared with a reference group from the background population, a difference that was no longer significant after adjusting for confounders (14). A Danish study of male offspring of mothers with diabetes found a slightly higher army rejection rate among adult offspring of women with diabetes (15). They also found significantly lower mean cognitive scores at draft board examinations and an inverse correlation between maternal $HbA_{1c}$ and offspring cognitive abilities ($n$ = 39).

A large population-based Swedish study recently examined the intelligence quotient (IQ) assessed at 18 years of age and found that male offspring of mothers with diabetes during pregnancy had a significantly lower IQ than other men at draft board examinations (16). However, no such association was found within sibships. This led the authors to conclude that the association between maternal diabetes in pregnancy and offspring cognitive outcome is more likely to be explained by familial characteristic than by intrauterine exposure. In addition, clinical studies examining cognitive function using different cognitive tests or developmental milestones have been published (9,17–19). Follow-up time is short (9,18) for some of the studies, and many of these studies did not differentiate between diabetes types (9,13,16–18). A few studies have found negative associations between maternal glycemic control during pregnancy and offspring cognitive outcome, whereas others have not (9,15,19). Thus, the extent to which extent type 1 diabetes and the glycemic control during pregnancy affect offspring cognitive development is not clear.

The aim of this study was to assess the consequences of a pregnancy complicated by pregestational type 1 diabetes on offspring school grades. We hypothesized that intrauterine hyperglycemia would be negatively associated with later offspring cognitive function. In addition, we examined the association between maternal $HbA_{1c}$ and offspring school grades.

## RESEARCH DESIGN AND METHODS

During 1992 to 1999, pregnancies in Danish women with type 1 diabetes were prospectively reported to a registry managed by the Danish Diabetes Association. Information about maternal demography, diabetes status, and pregnancy outcome was reported to the registry by local obstetricians in the eight hospitals in Denmark that, at the time, were responsible for antenatal care and delivery for pregnant women with type 1 diabetes. The information reported was obtained after the delivery of the child and was based on findings in the medical records. The coverage of cases from the reporting centers ranged from 75 to 93%. This was evaluated by cross-checking with local discharge registries and an insulin-prescription registry as described by Jensen et al. (20), who also reported deliveries from 1993 to 1999 in a study of perinatal complications.

We identified pregnancies in women with pregestational type 1 diabetes from 1992 until 1999. The inclusion criterion was delivery of a live-born child after 24 weeks of gestation. Each woman and her offspring were included as an index mother ($n$ = 991) and index child ($n$ = 1,326).

All index mothers and children were identified in the Danish Civil Registration System, and Statistics Denmark (www.dst.dk) assisted in identifying a control group with 100 control children for each index child. The matching criteria were control mother and index mother born the same year, and the control mother gave birth within $\pm$90 days of the index mother to a live-born child (control child) with the same sex as the index child. Matching was done by the greedy matching technique (21).

We excluded siblings and twin pregnancies from both cohorts and only included the index children with information on primary school grades and their matched control children (also with accessible grades). The final study population comprised 707 index children and 60,341 control children.

The study was approved by the Danish Data Protection Agency.

### School Grades

From Statistics Denmark we retrieved information about grades obtained by the index and control children at the end of their last year of primary school at the age of 15–16 years. The grades from all courses were included in the analyses. Information about grades was available from 2002 until the end of 2012.

Until 2007, a grading scale with 10 grades between 0 and 13 was used, and from 2007, a scale with 7 grades between $-3$ and 12 replaced the older scale. The grades from the older grading scale were transformed into the newer scale, and the mean grade was calculated. We adjusted our analyses for this transition between scales by applying the variable "original grading scale" (22).

### Parental Education

The educational status for parents of index and control children was retrieved from Statistics Denmark, which keeps information on educations achieved since 1981. We used the highest of the parents' education to classify the parental educational status. If the education was only known for one of the parents, this was used as the parental educational status. The three educational groups were *1*) primary or secondary school, *2*) vocational training or short-cycle higher education, and *3*) bachelor's degree or higher. For 12 index children and 1,049 control children, the educational status was not available for the mother or father, and their educational status was classified as missing.

### Gestational Age

From the Danish Medical Birth Registry we received information regarding gestational age at birth for 690 index children and 59,617 control children.

### $HbA_{1c}$, Pregnancy, and Neonatal Complications

For 602 index children, it was possible to retrieve information about $HbA_{1c}$ before and during pregnancy. One $HbA_{1c}$

measurement was reported each trimester to the registry. Local assays were used, and calibration was made afterward to a common standard as described by Jensen et al. (23). We were able to retrieve first trimester $HbA_{1c}$ for 585 pregnancies, and pregestational $HbA_{1c}$ was used as a surrogate in 14 cases. Third trimester $HbA_{1c}$ was accessible for 593 cases, and we used second trimester $HbA_{1c}$ as a surrogate in 25 cases. In a Danish guideline, the recommended $HbA_{1c}$ levels are <7% [53 mmol/mol] pregestationally, <6.5% [48 mmol/mol] during the first half of pregnancy, and <5.6% [38 mmol/mol] during the last half of pregnancy (24). We used these recommendations in the analyses.

It was possible to retrieve information on pregnancy complications and neonatal complications for most of the index children (Table 1), and we used this information to study possible associations with school performance. Maternal ketoacidosis was defined as plasma bicarbonate <15 mmol/L and hospitalization. Maternal hypoglycemia was defined as hypoglycemia requiring help from another person. Complications during pregnancy were defined as occurrence of one of the following: hydramnios (clinical diagnosis) and preeclampsia (blood pressure >140/90 mmHg and proteinuria). Neonatal complications were defined as the occurrence of one of the following: neonatal hypoglycemia (signs of hypoglycemia that disappeared after administration of glucose), jaundice (treated with phototherapy), transitory tachypnea (demanding assisted ventilation, such as continuous positive airway pressure >1 h postpartum), and infection (systemically treated).

**Table 1—Baseline characteristics of mothers with pregestational type 1 diabetes (index mothers), their children (index children), and matched control children**

| | Index children $n$ = 707 | Control children $n$ = 60,341 | $P$ value |
|---|---|---|---|
| Male sex, $n$ (%) | 324 (45.8) | 26,933 (44.6) | |
| Gestational age at birth (weeks) | 36.6 (25–41) | 39.6 (24–43) | <0.001* |
| Gestational age <34 weeks, $n$ (%) | 48 (7.0) | 598 (1.0) | |
| Gestational age <37 weeks, $n$ (%) | 204 (29.6) | 1,809 (3.0) | |
| Highest parental educational status, $n$ (%) | | | |
| Primary or secondary school | 71 (10.2) | 5,957 (10.1) | |
| Vocational training or short-cycle higher education | 389 (56.0) | 29,989 (50.6) | |
| Bachelor's degree or higher | 235 (33.8) | 23,346 (39.4) | 0.02† |
| Maternal age at birth of child (years) | 29.2 (4.8) | 29.3 (4.6) | |
| | Index mothers ($n$ = 707) | | $n$‡ |
| Pregestational BMI (kg/m$^2$) | 23.6 (17.8–42.3) | | 573 |
| Duration of diabetes (years) | 12.6 (0–36) | | 596 |
| Maternal age at debut of diabetes (years) | 16.0 (1–38) | | 596 |
| Parity | 1.5 (0–5) | | 597 |
| Maternal ketoacidosis, $n$ (%) | 10 (1.7) | | 589 |
| Maternal hypoglycemia, $n$ (%) | 75 (12.8) | | 587 |
| Complications during pregnancy, $n$ (%)§ | 167 (30.1) | | 555 |
| $HbA_{1c}$ (% [mmol/mol]) | | | |
| Pregestational | 7.9 (4.1–15.2) [63 (21–143)] | | 483 |
| First trimester | 7.5 (4.1–12.5) [58 (21–113)] | | 585 |
| Second trimester | 6.7 (4.2–11.2) [50 (22–99)] | | 580 |
| Third trimester | 6.8 (4.1–12.2) [51 (21–110)] | | 593 |
| Birth weight (g) | 3,520 (845–5,500) | | 604 |
| Apgar score after 5 min | 9.7 (1–10) | | 590 |
| Neonatal complications, $n$ (%)‖ | 237 (43.7) | | 542 |

Data are presented as mean and range or SD or as indicated. *$P$ value is obtained by Wilcoxon rank sum test. †Test for trend of educational distribution (modified Wilcoxon rank sum test). ‡Number with valid information. §Defined as occurrence of one of the following complications: hydramnios, 70 (12.6%); preeclampsia, 114 (20.5%). ‖Defined as occurrence of one of the following complications: neonatal hypoglycemia, 122 (22.5%); phototherapy-treated jaundice, 112 (20.6%); respiratory insufficiency, 88 (16.2%); infection (systemically treated), 40 (7.3%).

### Statistics

Baseline comparisons between the index children and control children were performed using the Wilcoxon rank sum test. Test for trend of parental educational level between index and control parents was analyzed using a modified Wilcoxon rank sum test (Table 1). We analyzed the difference in school grades between index and control children with a linear regression analysis, presenting the regression coefficient (β) with 95% CI to express the mean difference. Because of the matched design, we used robust standard error estimates. We adjusted this analysis for sex, original grading scale, and maternal age at delivery as linear and quadratic terms, and in a second analysis, we further adjusted for parental educational status. We also analyzed subgroups according to gestational age and glycemic control as assessed by recommended $HbA_{1c}$ levels (Supplementary Table 1).

The association between maternal $HbA_{1c}$ and school marks was analyzed among the index children. We used a linear regression model using school grades as the outcome measure. $HbA_{1c}$ was included as a continuous variable, and the regression coefficient corresponds to a one-percentage point increase in $HbA_{1c}$ (e.g., from 6% [42 mmol/mol] to 7% [53 mmol/mol]). We adjusted this analysis for sex, parity, original grading scale, maternal age at delivery, and parental educational status. We repeated this analysis, restricting it to children born after ≥37 gestational weeks (Table 2). In all analyses, we examined the residuals to check for violations of the assumptions for the regression analyses.

Birth weight, gestational age, complications during pregnancy, neonatal complications, and Apgar score were considered as possible mediators on the causal pathway between maternal diabetes and offspring cognitive function, and in an additional analysis, we separately included each of these variables with school grades as the outcome measure (Table 3). As above, we adjusted these analyses for sex, parity, original grading scale, maternal age at delivery, and parental educational status. Also, diabetes duration at delivery, sex, parity, parental educational status, maternal ketoacidosis, and maternal hypoglycemia were separately included in a regression analysis of potential predictors of offspring primary school grades (Table 3).

**Table 2—Association between $HbA_{1c}$ and average school grades for offspring born to mothers with type 1 diabetes**

| $HbA_{1c}$ measurement in relation to pregnancy | All children included | | | | Children born after GA >37 weeks | | | |
|---|---|---|---|---|---|---|---|---|
| | *n** | β | 95% CI | *P* value | *n** | β | 95% CI | *P* value |
| Pregestational | 483 | −0.13 | −0.25 to −0.01 | 0.04 | 288 | −0.10 | −0.25 to 0.05 | 0.21 |
| 1st trimester | 585 | −0.24 | −0.37 to −0.11 | <0.001 | 357 | −0.22 | −0.38 to −0.06 | 0.01 |
| 2nd trimester | 580 | −0.19 | −0.36 to −0.02 | 0.03 | 354 | −0.20 | −0.43 to 0.02 | 0.08 |
| 3rd trimester | 593 | −0.31 | −0.47 to −0.14 | <0.001 | 364 | −0.33 | −0.55 to −0.10 | 0.005 |

Results from linear regression analysis are given as regression coefficient (β) per 1% change in $HbA_{1c}$ adjusted for sex, parity, maternal age at birth, original grading scale, and parental educational status. GA, gestational age. *Number of index children.

Statistical analyses were done in Stata 13.1 for Windows, and *P* values of <0.05 were considered significant.

## RESULTS

Statistics Denmark retrieved school grades for 707 index children and 60,341 control children matched to the included index children (Table 1). The gestational age at birth was ~3 weeks less for index children than for the control children. The combined parental educational status was also lower for the index children than for the control children.

The average school grades for index children were 6.37 (SD 2.34) and for control children were 6.52 (SD 2.36). After adjustment for sex, maternal age, and the original grading scale, the difference was β = –0.13 (95% CI = –0.30 to 0.03, *P* = 0.12). Further adjusting for parental educational status did not change this result substantially (β = –0.07, 95% CI = –0.23 to 0.09, *P* = 0.37). We repeated the analysis dividing the index children into groups according to gestational age ≥37 weeks and <37 weeks and according to maternal glycemic control before and during pregnancy. Index children born before and after 37 gestational weeks obtained similar average grades compared with the matched control children (β = –0.02 [95% CI = –0.21 to 0.17], *P* = 0.81 and β = –0.08 [–0.37 to 0.20], *P* = 0.57).

Repeating the analyses using the Danish recommendations for $HbA_{1c}$ levels during pregnancy, we found that index children born to mothers achieving good glycemic control tended to obtain higher average school grades compared with the matched control children (Supplementary Table 1). Especially index children born to mothers with third trimester $HbA_{1c}$ <5.6% [38 mmol/mol] obtained higher average grades (β = 0.52 [95% CI = 0.09 to 0.96]) (Fig. 1). The opposite applied to index children born to mothers with inadequate glycemic control ($HbA_{1c}$ in the highest quartile before and/or during pregnancy). These children obtained lower average mean grades compared with the matched control children (β ranging from –0.42 [95% CI = –0.79 to –0.04] for offspring of women with pregestational $HbA_{1c}$ in the highest quartile to −0.58 [–0.92 to –0.23] for offspring of women with third trimester $HbA_{1c}$ in the highest quartile to –0.65 [–0.99 to –0.31]) when the maternal first trimester $HbA_{1c}$ was in the highest quartile (Supplementary Table 1).

We saw a strong and significant association between educational level and glycemic control among the index mothers. Of the women with $HbA_{1c}$ <7.0% [53 mmol/mol] before gestation, 37.2% of the parents held a bachelor's degree or higher. For women with a $HbA_{1c}$ >8.8% [73 mmol/mol] in the same gestational period, only 13.4% of the parents had an education equivalent to a bachelor's degree or higher. These numbers were 27.3%

**Table 3—Predictors of average school grades for children born to mothers with type 1 diabetes**

| Potential predictors | β | 95% CI | *P* value |
|---|---|---|---|
| Diabetes duration at delivery (years) | 0.01 | −0.02 to 0.03 | 0.50 |
| Maternal age (years) | | | <0.001 |
| <25 | −0.73 | −1.25 to −0.21 | |
| 25–29 | 0.00 | (reference) | |
| 30–34 | 0.33 | −0.11 to 0.76 | |
| 35+ | 0.83 | 0.26 to 1.40 | |
| Sex (female vs. male) | 0.94 | 0.60 to 1.29 | <0.001 |
| Parity (≥2 vs. 1) | −0.46 | −0.79 to −0.14 | 0.01 |
| Parental educational status | | | |
| Primary or secondary school | −1.19 | −1.80 to −0.57 | <0.001 |
| Vocational training or short-cycle higher education | 0.00 | (reference) | |
| Bachelor's degree or higher | 1.22 | 0.84 to 1.60 | <0.001 |
| Maternal ketoacidosis (yes vs. no) | −0.30 | −1.64 to 1.04 | 0.66 |
| Maternal hypoglycemia (yes vs. no) | −0.11 | −0.63 to 0.42 | 0.69 |
| Complications during pregnancy* | −0.19 | −0.59 to 0.21 | 0.36 |
| Neonatal complications† | −0.25 | −0.62 to 0.13 | 0.20 |
| Birth weight (g) | | | |
| <3,000 | −0.30 | −0.73 to 0.14 | 0.19 |
| 3,000–3,999 | 0.00 | (reference) | |
| >4,000 | −0.01 | −0.42 to 0.40 | 0.96 |
| Gestational age (weeks) | | | |
| 24–33 | −0.06 | −0.72 to 0.61 | 0.87 |
| 34–36 | 0.06 | −0.32 to 0.45 | 0.75 |
| 37–41 | 0.00 | (reference) | |
| Apgar <7 at 5 min | −0.11 | −1.68 to 1.47 | 0.89 |

The regression coefficients (β) from a univariate linear regression analysis represent differences in school grades adjusted for maternal age at birth, sex, parity, original grading scale, and parental educational status. *Defined as the occurrence of one of the following complications: hydramnios, 70 (12.6%); preeclampsia, 114 (20.5%). †Defined as occurrence of one of the following complications: neonatal hypoglycemia, 122 (22.5%); phototherapy-treated jaundice, 112 (20.6%); respiratory insufficiency, 88 (16.2%); infection (systemically treated), 40 (7.3%).

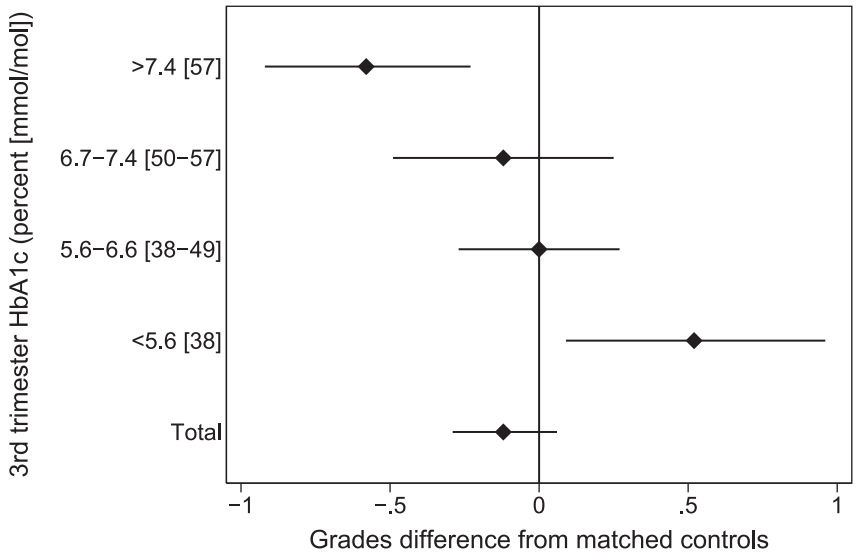


**Figure 1**—Difference in average school grades between offspring born to women with type 1 diabetes and the matched control children, by maternal third trimester $HbA_{1c}$ level, adjusted for parental educational status. 95% CIs with robust standard errors.

versus 16.7% for first trimester $HbA_{1c}$ and 15.7% versus 13.6% for third trimester $HbA_{1c}$ (Supplementary Table 2).

Among the index children, we analyzed the association between maternal $HbA_{1c}$ and school grades. The average grades when finishing primary school were associated with maternal $HbA_{1c}$ pregestationally (β = –0.13 [95% CI = –0.25 to −0.01]) and throughout pregnancy (β ranging from –0.19 [–0.36 to –0.02] for second trimester $HbA_{1c}$ to –0.31 [–0.47 to –0.14] for third trimester $HbA_{1c}$) when adjusted for confounders including parental educational status (Table 2). In an additional analysis only including children born after 37 weeks of gestation, the association between average grades and maternal $HbA_{1c}$ was attenuated but still significant for $HbA_{1c}$ measurements in first and third trimester (β= –0.22 [–0.38 to –0.06] and –0.33 [–0.55 to –0.10]).

Among potential predictors of later average school grades, young maternal age (β= –0.73 [95% CI = –1.25 to –0.21]), parity >1 (β= –0.46 [–0.79 to –0.14]), and no parental education beyond secondary school (β = –1.19 [–1.80 to –0.57]) were associated with lower average grades (Table 3). Female sex (β = 0.94 [0.60 to 1.29]) and parental educational status corresponding to a bachelor's degree or higher (β= 1.22 [0.84 to 1.60]) were associated with higher average grades (Table 3). Birth weight, gestational age, complications during pregnancy, neonatal complications, and Apgar score were considered to be possible mediators on the pathway between maternal type 1 diabetes during pregnancy and offspring cognitive function, but none were associated with offspring average school grades (Table 3) and neither was maternal duration of diabetes, maternal ketoacidosis, nor maternal hypoglycemia.

## CONCLUSIONS

In this large study of offspring born to mothers with pregestational type 1 diabetes, we found that the offspring achieved similar average grades when finishing primary school compared with matched control offspring from the background population. We also found quite divergent academic achievement dependent on maternal $HbA_{1c}$ before and during pregnancy.

Among offspring born to mothers achieving good glycemic control, these tended to obtain better average grades than the matched control offspring, and offspring born to mothers with the lowest $HbA_{1c}$ during the third trimester obtained substantially higher grades compared with the matched control offspring. Offspring born to mothers with the poorest glycemic control pregestationally or during pregnancy received considerably lower average grades than the matched control offspring.

Among offspring born to mothers with type 1 diabetes, $HbA_{1c}$ measured before and during pregnancy was negatively associated with the later obtained school grades. Young maternal age, male sex, multiparity, and short parental education were also important predictors of low school grades among the index children. Neither complications during pregnancy, birth weight, gestational age, diabetes duration, maternal ketoacidosis, maternal hypoglycemia, low Apgar score, nor neonatal complications did to the same extent predict offspring school grades. Nielsen et al. (15) previously described a similar association between $HbA_{1c}$ and offspring cognitive outcome in a smaller study; however, they did not differentiate between diabetes types or adjust for socioeconomic status.

The recommended $HbA_{1c}$ level presently used in Denmark is <7% (53 mmol/mol) pregestationally, <6.5% (48 mmol/mol) during the first half of pregnancy, and <5.6% (38 mmol/mol) during the last half of pregnancy (24,25). We found that offspring of women achieving these target ranges obtained equally good or better average grades compared with the matched control offspring after adjusting for parental education. Conversely, offspring of the women with the poorest glycemic control achieved considerably lower average grades than the control offspring.

We found strong associations between parental education and glycemic control, between parental education and school grades, and between glycemic control and school grades, even after adjustment for parental education. The parents' educational status reflects their intellectual and social resources, which through inheritance and childhood environment affect the children's intellectual and social development (26,27). The finding of a strong association between glycemic control and obtained school grades, even after adjustment for parental education among the index children, has at least two possible explanations. First, maternal glycemic control may influence development of the fetal brain directly. Second, the ability to cope with a complex chronic disease, such as type 1 diabetes, may signal social and intellectual resources beyond what is explained by the formal educational status; resources that also affect the upbringing of a child. These two explanations could also work in concert.

Few of our index mothers reached the present recommended $HbA_{1c}$ level, and we therefore assume that most of the

index children were exposed to higher intrauterine levels of glucose compared with the control children. If maternal glycemic control directly influences the fetal brain development, we would have expected to find an overall difference in grades between the index children and the control children. This was not the case. However, the absence of this result does not rule out an effect of maternal glycemic control on offspring cognitive outcome, and when studying offspring of women in each end of the $HbA_{1c}$ scale, we found significant differences in grades comparing these children with the matched control children. But, among these two rather diverse groups of index mothers, not only glycemic control but also parental educational status, genes, and maternal treatment compliance differ, and we are not able to estimate how much of the observed differences is due to the direct effect of a hyperglycemic environment and how much is due to genetic and social circumstances.

We show that offspring born to women who achieved the recommended $HbA_{1c}$ levels obtained equally good or better average grades compared with the matched control children. These offspring were, due to the low $HbA_{1c}$ of their mothers, exposed to almost similar glucose levels as the matched control children. The finding of an even better academic performance in this group of children indicates that maternal organizational capacities or executive functional skills contribute to offspring cognitive function. This is an encouraging result when contemplating future guidance and treatment of pregnant women with type 1 diabetes. Furthermore, the results of the current study can be used in identifying the women with type 1 diabetes and their offspring who would be most likely to benefit from further guidance in respect to glycemic control during pregnancy and to later academic difficulties of the offspring.

Any measure of socioeconomic status only approximately reflects the intellectual, social, and material resources of a family. We used the parents' educational level because it is considered a very relevant predictor of the children's cognitive and social development (28). It also has the important advantage of being a relatively stable measure, whereas measures based on current occupation and income tends to vary over time.

In 1991, Rizzo et al. (29) found an association between offspring intelligence and maternal metabolism illustrated by β-hydroxybutyrate. In the current study, we could not find an association between maternal ketoacidosis and later offspring school grades, probably because only 10 women were diagnosed with ketoacidosis during pregnancy and we had no information on maternal β-hydroxybutyrate levels. Also an Apgar score of $<7$ at 5 min after birth has previously been associated with school performance at 16 years of age among children born in Sweden between 1973 and 1986 (30), a result we could not replicate among our diabetes-exposed index children. Studies after the Dutch famine during World War II provide an example of a different kind of an adverse pregnancy environment and the potential offspring cognitive consequences. Similar to our findings, these studies also describe no overall difference in cognitive function and a strong association between socioeconomic status and offspring cognitive outcome (31,32).

One of our study's strengths is that it includes a large cohort of prospectively studied offspring of women with pregestational type 1 diabetes. Our cohort is well characterized, and no mothers with type 2 diabetes or gestational diabetes were included. The coverage level is high and was cross-checked with local discharge registries and an insulin-prescription registry to ensure that the register was not contaminated with false-positive cases.

Inclusion in the study required access to the offspring's school grades when finishing the Danish primary school. Because offspring of women with type 1 diabetes have an increased risk of perinatal morbidity, one could speculate that long-term cognitive consequences of a complicated type 1 diabetes pregnancy are so grave that the offspring would attend a special school or not be able to complete primary school. This, along with inaccessible $HbA_{1c}$ for some of the pregnancies and the use of school grades and parental educational status as a proxy for cognitive function, must be considered as possible limitations of the current study. Owing to the nature of the original Diabetes Association Registry, we only had information on offspring born after the mother was diagnosed with type 1 diabetes. Using Fraser et al. (16) as example, the current study could have benefitted from information on older siblings born before the maternal type 1 diabetes diagnosis in an attempt to distinguish between the influences of a hyperglycemic intrauterine environment and socioeconomic effect on offspring cognitive function. Unfortunately, obtaining this information was not possible with our setup.

Also as the offspring mature and become adults, the use of registry data describing income, educational status, and employment status would be useful in a description of the potential influence not only of a hyperglycemic environment, but also the effect of differences in gestational age as well as parental educational status on offspring socioeconomic status extending beyond primary school.

It is possible that the women with the poorest glycemic control are not regularly seen during pregnancy and that they are therefore underrepresented in the register, but this would not affect the main estimates in this study. It is also possible that some of the control mothers have diabetes. This, however, would only lead to an underestimation of the association between maternal diabetes and offspring cognitive outcome.

The current guidelines for maternal glycemic control reflect the increasing knowledge of the physiological changes of $HbA_{1c}$ during pregnancy (33). During the 1990s, an $HbA_{1c}$ level of $<7\%$ (53 mmol/mol) during pregnancy was considered acceptable glycemic control, and as a result of the current guidelines, we expect that pregnant women with type 1 diabetes today obtain lower $HbA_{1c}$ levels than the women included in our study. Secher et al. (34) described a tighter glycemic regulation among pregnant women with type 1 diabetes during 2009 to 2011 than among the women included in our study. They measured $HbA_{1c}$ in a study in which participants used continuous glucose monitoring during pregnancy and reported substantially lower first trimester $HbA_{1c}$ of 6.3–6.8% (45–51 mmol/mol) and third trimester $HbA_{1c}$ of 6.0–6.2% (42–44 mmol/mol) (34). Therefore, we would expect a different composition of our $HbA_{1c}$ groups today. This could potentially change the association between $HbA_{1c}$ and offspring cognitive outcome and is an obvious hypothesis for future research.

In conclusion, children born to mothers with pregestational type 1 diabetes obtained similar average grades when finishing the Danish primary school compared

with the matched control children. However, there was a strong association between good maternal glycemic control and the average grades obtained by the children. It is, however, uncertain whether this association reflects a direct causal influence of the quality of maternal glycemic control on the cognitive development of children of women with type 1 diabetes.

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**Author Contributions**. P.D. and H.B.-N. contributed to the establishment of the original registry. P.D. and D.M.J. contributed to data collection. S.K., T.D.C., Z.V., B.B., P.D., H.B.-N., D.M.J., and C.H.G. contributed substantially to the conception and design of the study. S.K., S.J., and C.H.G. analyzed the data. S.K. drafted the manuscript and designed the tables. All authors were involved in the interpretation of the data, critically revised the article, and approved the final version for publishing. All authors had full access to the data in the study, with the restrictions set by Statistics Denmark, and take full responsibility for the integrity of the data and the accuracy of the data analysis. S.K. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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