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Academic Performance in Adolescents Born to Mothers With Gestational Diabetes—A National Danish Cohort Study

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Abbreviations: AGA, appropriate for gestational age; aOR, adjusted odds ratio; GDM, gestational diabetes mellitus; GPA, grade point average; ICD-10, International Classification of Diseases and Related Health Problems 10th revision; LGA, large for gestational age; O-BP, offspring from background population; O-GDM, offspring exposed to gestational diabetes mellitus; OGTT, oral glucose tolerance test; SGA, small for gestational age.

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Abstract

Context: The prevalence of gestational diabetes mellitus (GDM) is increasing, and intrauterine hyperglycemia is suspected to affect offspring cognitive function.

Objective: We assessed academic performance by grade point average (GPA) in children aged 15 to 16 years at compulsory school graduation, comparing offspring exposed to GDM (O-GDM) with offspring from the background population (O-BP).

Methods: This register-based, cohort study comprised all singletons born in Denmark between 1994 and 2001 (O-GDM: n = 4286; O-BP: n = 501 045). Standardized and
Internationally comparable GPAs were compared in univariate and multivariable linear models. Main outcome measures included the adjusted mean difference in GPA. We also analyzed the probability of having a high GPA, a GPA below passing, and no GPA registered.

**Results:** O-GDM had a GPA of 6.29 (SD 2.52), whereas O-BP had a GPA of 6.78 (SD 2.50). The adjusted mean difference was –0.36 (95% CI, –0.44 to –0.29), corresponding to a Cohen's $D$ of 0.14. O-GDM had a lower probability of obtaining a high GPA (adjusted odds ratio [aOR] 0.68; 95% CI, 0.59 to 0.79), while their risk of obtaining a GPA below passing was similar to O-BP (aOR 1.20; 95% CI, 0.96 to 1.50). O-GDM had a higher risk of not having a GPA registered (aOR 1.38; 95% CI, 1.24 to 1.53).

**Conclusion:** Academic performance in O-GDM was marginally lower than in O-BP. However, this difference is unlikely to be of clinical importance.

**Key Words:** academic performance, cognitive development, diabetes in pregnancy, gestational diabetes mellitus, long-term outcomes in offspring

Globally, the prevalence of gestational diabetes mellitus (GDM) is rapidly increasing. In 2017 the International Diabetes Federation estimated that 14% of all children worldwide were born to mothers with GDM; in Denmark the corresponding number was 4.9% in 2018 (1, 2).

As glucose passes the placenta, maternal hyperglycemia leads to intrauterine hyperglycemia, and subsequently hyperinsulinemia, which affects fetal growth (3). This leads to adverse perinatal outcomes including preterm birth and macrosomia (4, 5). Long-term implications include increased risk of offspring developing obesity and type 2 diabetes (6, 7). Additionally, diabetes during pregnancy is suspected to affect offspring cognition (8, 9). In animal studies, diabetes during pregnancy has been linked to morphological changes in the limbic system (10, 11) and impaired dendritic development—possibly through altered insulin-like growth factor-I/insulin receptor expression (12). Also, one animal study found maternal diabetes to negatively affect performance during functional tasks in offspring (13).

To try to assess whether diabetes during pregnancy affects the development of the human brain, some studies have examined electrophysical changes (electroencephalography) (14, 15), while others have focused on IQ tests and academic performance. Results have been diverging, with some studies showing adverse outcomes (16-19), whereas others have found no such association (20-23). One study even found GDM to be positively associated with IQ in offspring (24).

In Denmark basic education is mandatory by law, and public and private educational institutions both are obligated to report grade points from compulsory school graduation to a national register. This provides a unique opportunity to assess academic performance as an expression of cognitive development in a large population of offspring exposed to GDM.

The aim of this paper was to assess academic performance in adolescents aged 15 to 16 years comparing grade points at compulsory school graduation in offspring exposed to gestational diabetes mellitus (O-GDM) with offspring from the background population (O-BP), while adjusting for relevant confounders and exploring into potential effect modification and mediating factors.

**Materials and Methods**

**Study Population and Data Sources**

This study was a national register-based cohort study including all children born in Denmark from January 1, 1994 to December 31, 2001. The cohort was established based on the Danish Medical Birth Registry, the Danish Patient Registry, and sociodemographic registries from Statistics Denmark. Based on a personal identification number, we were able to crosslink information on maternal, fetal, and neonatal health with sociodemographic covariates. The cohort consisted of 4286 O-GDM and 501 045 O-BP. We excluded all twins ($n = 19 497$) and offspring that died ($n = 3159$) or emigrated ($n = 12 306$) between birth and the estimated time of graduation. Data on grade points were extracted in 2017 to ensure that the offspring were at least age 15 to 16 years and the majority thereby had graduated compulsory school.

In Denmark registry-based studies, in which individuals cannot be identified, do not require approval form a scientific ethics committee. This study was approved by the Danish Data Protection Agency (DT-journal No. 2012-58-0004; local journal No. AHH-2016-033; I-suite No. 04790).

**Identification of Offspring Exposed to Gestational Diabetes Mellitus**

O-GDM were identified through their mothers. Mothers with GDM were identified in the Danish Patient Register.
as patients assigned with the International Classification of Diseases and Related Health Problems 10th revision (ICD-10) code O244 for GDM between 280 days before the day of birth until 30 days after the day of birth. GDM was diagnosed following a 75-g oral glucose tolerance test (OGTT). During our study period both 2- and 3-hour OGTTs were used. The 2-hour test was diagnostic for GDM if capillary or venous plasma glucose was greater than or equal to 9 mmol/L after 2 hours. For venous plasma the 3-hour OGTT was considered abnormal if 2 or more glucose values exceeded the following: 6.2 mmol/L at 0 minutes, 10.9 mmol/L at 30 minutes, 11.1 mmol/L at 60 minutes, 9.2 mmol/L at 90 minutes, 8.9 mmol/L at 120 minutes, 8.2 mmol/L at 150 minutes, and 7.3 mmol/L at 180 minutes. GDM screening was based on anamnestic risk factors, urine analyses, and capillary/venous plasma fasting glucose levels (25).

Academic Performance

Data on academic performance were extracted from Statistics Denmark. In Denmark 10 years of education is compulsory by law. Compulsory school starts at age 6 years when children enter preschool followed by 9 years of primary and secondary school. Public and private schools are similarly structured and are completed with a final test when the children are age 15 to 16 years. Only around 2% of schools do not have this test (26). The final test includes the following mandatory school courses: Danish (oral and written), mathematics (written), English (oral), and physics/chemistry (oral). The written tests are the same nationally, while the topic of examination varies for oral tests. Based on the tests, grade points are given for each course. Furthermore, the teacher gives an additional grade point for each course reflecting the general academic level throughout the year.

Outcomes

Grade points are marked by a 7-point grading scale (–3, 00, 02, 4, 7, 10, 12) with the average grade point being 7 (corresponding to the average score C on the European Credit Transfer System scale). We report course-specific grade points as well as grade point average (GPA) based both on the final test and the corresponding grades from the academic level throughout the year. If offspring did not have all grade points registered, the remaining grade points were used to calculate the GPA.

Our primary outcome was the difference in GPA between O-GDM and O-BP. Secondary outcomes included the probability of having a high GPA (≥ 10) and the risk of having a GPA below passing level (< 2) as well as the risk of not having a GPA registered. For offspring not registered with a GPA, we investigated if they had a higher prevalence of cerebral palsy. We additionally explored the impact of potential mediating factors and effect modification.

Covariates

Potential confounders and mediators were chosen based on the current literature on factors influencing school grades (27, 28).

Maternal covariates included maternal age coded as a continuous variable, parity as a 2-category variable (nulliparous, multiparous), mode of conception as a 2-category variable (assisted reproductive technologies, spontaneous), hypertensive disorders in pregnancy as a 2-category variable (yes, no), mode of delivery as a 2-category variable (cesarean delivery, vaginally), maternal smoking during pregnancy as a 2-category variable (yes, no), and maternal nationality as a 2-category variable (mother not born in Denmark, mother born in Denmark). Mothers diagnosed with hypertensive disorders in pregnancy were defined as women assigned with the ICD-10 codes O10 to O16.

Sociodemographic covariates included area of residence coded as a 5-category variable (central and south Zealand, Copenhagen and north Zealand, southern of Jutland and Funen, central Jutland, north of Jutland [reference]), co-habitating parents at the time of graduation as a 2-category variable (yes, no), and maternal educational level as a 4-category variable (low [reference], middle, high, highest).

Offspring covariates included year of graduation coded as a continuous variable, birth weight as a 3-category variable (low [< 2500 g], normal [2500 g-4000 g] [reference], high [≥ 4000 g]), gestational age as a 3-category variable (very preterm birth [≤ 33 + 6 weeks], preterm birth [34 + 0 to 36 + 6 weeks], term birth [≥ 37 + 0 weeks] [reference]), weight according to gestational age as a 3-category variable (small for gestational age [SGA], appropriate for gestational age [AGA] [reference], large for gestational age [LGA]), offspring sex as a 2-category variable (male, female), and cerebral palsy as a 2-category variable (yes, no).

SGA was defined as less than –2 SD and LGA as greater than +2 SD from the expected sex-specific birth weight for the given gestational age (29). Until 1996 the Danish medical birth registry registered gestational age in weeks only. From 1997 and onward gestational age was registered in days. To maintain accurate analyses only offspring born during 1997 to 2001 were included in analyses stratifying according to SGA/AGA/LGA. Offspring diagnosed with cerebral palsy were identified as offspring assigned with the ICD-10 codes G80 to G83 between birth and age 10 years.
Statistics

Descriptive statistics of maternal and offspring characteristics are presented as means and SD or absolute numbers and percentages. GPA and course-specific grade points were compared using linear mixed model analyses to account for correlation in GPA within siblings. This was performed both in univariate and multivariable models. Multivariable models were created in a 2-step manner: model 1 was adjusted for maternal age, parity, mode of conception, year of graduation, and offspring sex. Model 2 was adjusted for the same variables as model 1 as well as variables associated with socioeconomic status: maternal smoking during pregnancy, maternal nationality, area of residence, cohabiting parents, and maternal educational level at the time of graduation. To assess the clinical impact of the effect of GDM on academic performance, we calculated Cohen’s $D$ by dividing the fully adjusted mean difference in GPA with the SD.

We considered hypertensive disorders in pregnancy, mode of delivery, birth weight, and gestational age as potential mediators on the causal pathway between GDM and academic performance, which we explored in separate analyses by adding them one by one to model 2. Additionally, maternal-, sociodemographic-, and offspring-related covariates were explored as potential effect modifiers in stratified analyses comparing GPA in O-GDM and O-BP both in univariate and multivariable linear mixed model analyses for each stratum. Furthermore, potential effect modifiers were subsequently added one by one in interaction analyses. Secondary outcomes (probability of having a high GPA (≥ 10), risk of having a GPA below passing level (< 2), risk of not having a GPA registered) were analyzed in logistic regression models using generalized estimating equations to account for correlation in GPA within siblings. All analyses were adjusted according to models 1 and 2.

To account for typing errors in the registries, recordings were excluded if not in the following intervals: gestational age 140-308 days, birth weight 200-6500g, and maternal parity 0-20.

All analyses were conducted using RStudio, version 3.6.1. The lme4 and MASS packages were used for linear mixed models and logistic regression analyses, respectively (30, 31).

Results

In this study, 4286 O-GDM and 501 045 O-BP were eligible. For the total cohort (birth year 1994-2001) GPA at compulsory school graduation was registered in 3777 O-GDM (88.1%) and 459 055 O-BP (91.6%). Of offspring registered with a GPA, 5.7% of O-GDM and 4.4% of O-BP missed a grade point in at least one course.

Maternal, Sociodemographic, and Offspring Background Characteristics

Mothers with GDM were older, more likely to be multiparous, and had a higher prevalence of hypertensive disorders in pregnancy. They additionally were more likely to have a cesarean delivery but were less likely to smoke during pregnancy. Mothers with GDM were more often born outside Denmark and area of residence in Denmark varied between the 2 groups. Furthermore, mothers with GDM had a lower educational level at the time of offspring graduation from compulsory school (Table 1). O-GDM had a higher mean birth weight and were more likely to be born preterm. O-GDM were less likely to be born SGA, and more likely to be born LGA (see Table 1).

Missing data on covariates reduced sample size by 0.9% (n = 4084) in model 1 and 20.5% (n = 95 032) in model 2. If smoking during pregnancy was excluded, the sample size was reduced by only 1.7%. Removing smoking during pregnancy did not change the main outcome. No attempt was made to impute missing data.

Primary Outcome

GPA was 6.29 (2.52 SD) for O-GDM and 6.78 (2.50 SD) for O-BP with a crude mean difference of −0.38 (95% CI, −0.45 to −0.30). When adjusting according to model 1 the mean difference increased to −0.57 (95% CI, −0.64 to−0.50), while the fully adjusted mean difference (model 2) was −0.36 (95% CI, −0.44 to−0.29) (Table 2). We calculated Cohen’s $D$ and found the effect size of GDM on the adjusted mean difference in GPA to be 0.14. The adjusted mean difference in course specific grade points is listed in Table 2.

Potential Mediators

Adding potential mediators to model 1 did not change the adjusted mean difference in GPA when comparing O-GDM and O-BP (data not shown).

Potential Effect Modification

Stratified analyses showed little difference regarding the effect of GDM on offspring GPA when comparing different strata (Table 3). However, among offspring born with low birth weight (< 2500 g) the adverse effect of...
GDM on offspring GPA seemed more pronounced than in other birth weight strata (see Table 3).

In interaction analyses we confirmed that the negative effect of GDM on offspring GPA was increased in offspring born with low birth weight. When looking at offspring born with low birth weight, the difference between GDM and O-GDM increased by –0.55 (95% CI, –0.99 to –0.11) compared to offspring born with normal birth weight. There were no significant interactions between the effect of GDM on offspring GPA and other maternal-, sociodemographic-, or offspring-related covariates (Table 4).

**Secondary Outcomes**

O-GDM had a lower probability of receiving a high GPA compared with O-BP (adjusted odds ratio [aOR] 0.68; 95% CI, 0.59-0.79), while the risk of obtaining a GPA below passing level was not significantly different (aOR 1.20; 95% CI, 0.96-1.50) (Table 5). In total, 509 (11.9%) O-GDM and 41 990 (8.4%) O-BP did not have any grade point registered at compulsory school graduation, corresponding to an aOR of 1.38 (95% CI, 1.24-1.53). Maternal, sociodemographic-, and offspring characteristics of O-GDM and O-BP not registered with a grade at compulsory school graduation are shown in Table 6. There was no significant difference in the prevalence of cerebral palsy in the 2 groups (aOR 1.09; 95% CI, 0.61-1.94).

**Discussion**

In this national register-based cohort study including all singletons born during 1994 to 2001, we found crude and adjusted GPA to be slightly lower in O-GDM compared to O-BP. The lower GPA in O-GDM did not seem to be mediated through more prevalent adverse obstetric- or offspring-related outcomes following GDM pregnancies. However, there was a significant interaction between GDM exposure and birth weight below 2500 g as the difference in GPA between the 2 groups increased when looking at offspring born with low birth weight compared to offspring born with normal birth weight. There was no significant interaction with either
prematurity or SGA. However, there was a trend suggesting that an increased degree of prematurity could affect the effect of GDM on academic performance, and this interaction might have been significant if more very preterm O-GDM were included. According to the estimates it seems likely that low birth weight indicates some degree of prematurity and impaired fetal growth, which has previously been found to be associated with impaired cognitive function (32).

Furthermore, O-GDM were less likely to achieve a high GPA, but were not at increased risk of achieving a GPA below passing level. O-GDM were more likely not to have a GPA registered, meaning they did not have any grades or test scores registered in any course at compulsory school graduation, indicating that they did not complete compulsory school. As mentioned earlier, there were differences in background characteristics when comparing O-GDM to O-BP (see Table 1); this also applied to offspring not registered with a GPA (Table 6). Generally, it was the same parameters that differed as in the total study population. The risk of cerebral palsy was similar in O-BP and O-GDM.

### Strengths and Limitations

A strength of this study is its national cohort design including complete birth cohorts for 8 years. Furthermore, data from the Danish registries are prospectively collected, hold important information on confounders, and are generally of high validity (33, 34). Large register-based studies minimize the risk of selection bias and missing data. Only 0.9% of the cases were excluded for missing information in analyses including covariates from model 1. Overall, 20.5% of cases were excluded when adding variables related to sociodemographic status to our analyses (model 2). This was mainly due to missing information on smoking during pregnancy. We were able to adjust for multiple parameters related to sociodemographic status. However, residual confounding is possible, and inadequate adjustments related to sociodemographic status might have led us to overestimate the negative effect of GDM on academic performance. This is supported by a study from India that found GDM to be associated with higher IQ in offspring (24). In India GDM is associated with high socioeconomic status, whereas the opposite applies in Denmark. Furthermore, we were not able to adjust for maternal body mass index, paternal educational level, or parental IQ.

We did not have information on the severity of GDM such as insulin dependence or glycated hemoglobin A1c levels. Thus we were not able to confirm previous findings suggesting a dose-dependent effect of maternal hyperglycemia on offspring cognitive function (23, 35).

In Denmark it is estimated that around 68% of all GDM pregnancies are treated with diet only and do not have a need for insulin treatment (36). Because of this, we expect the level of intrauterine hyperglycemia to be relatively mild in our population, which would tend to underestimate the true effect of GDM on offspring cognitive development.

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### Table 2. Grade point average and course-specific grade points at compulsory school graduation. Given as means as well as crude and adjusted mean differences

| Course-specific grade points | Grade point average (SD) | O-GDM vs O-BP |
|-----------------------------|--------------------------|---------------|
|                             | O-GDM (n = 3777)         | O-BP (n = 459,055) |
|                             | Crude mean difference (95% CI) | Adjusted mean difference (95% CI) | Adjusted mean difference (95% CI) |
| Grade point average         | 6.29 (2.5)               | 6.78 (2.5)     | -0.38 (-0.45 to -0.30) | -0.57 (-0.64 to -0.50) | -0.36 (-0.44 to -0.29) |
| Course-specific grade points| Danish                   | 6.25 (2.5)     | 6.74 (2.5)     | -0.39 (-0.47 to -0.31) | -0.58 (-0.65 to -0.50) | -0.39 (-0.47 to -0.31) |
|                             | Mathematics              | 6.26 (3.0)     | 6.83 (3.0)     | -0.48 (-0.57 to -0.39) | -0.63 (-0.72 to -0.54) | -0.37 (-0.47 to -0.27) |
|                             | English                  | 6.76 (3.2)     | 7.13 (3.1)     | -0.26 (-0.36 to -0.16) | -0.54 (-0.63 to -0.44) | -0.34 (-0.44 to -0.23) |
|                             | Physics/Chemistry         | 6.17 (3.1)     | 6.56 (3.1)     | -0.32 (-0.42 to -0.22) | -0.53 (-0.63 to -0.43) | -0.30 (-0.41 to -0.19) |

Grade point average was compared using linear mixed model analyses to account for correlations in grade point average within siblings. Model 1 adjusted for maternal age, parity, mode of conception, year of graduation, and offspring sex. Model 2 adjusted for covariates in Model 1 as well as maternal smoking during pregnancy, maternal nationality, area of residence, cohabiting parents at time of graduation, and maternal educational level.

Abbreviations: GDM, gestational diabetes mellitus; O-BP, offspring from background population; O-GDM, offspring of women with gestational diabetes mellitus.
Previous Studies

Several studies have investigated cognitive function in O-GDM. The vast majority of the studies have looked at offspring aged 4 months to 8 years (19, 24, 37-39). Results have been diverging and generally, studies are small. To our knowledge only a few studies have looked at academic
Table 4. Interaction analyses. The first column shows the effect of gestational diabetes mellitus (GDM) on grade point average in the part of the population with and without the potential effect modifier, while the second column shows the interaction between GDM and the potential effect modifier.

| Potential effect modifier | Effect of GDM on adjusted mean difference with effect modifier (95% CI) | Interaction (95% CI) |
|---------------------------|---------------------------------------------------------------------|---------------------|
| Parity                    |                                                                     |                     |
| Nulliparous               | –0.33 (–0.46 to –0.19)                                              | 0.05 (–0.11 to –0.22) |
| Multiparous               | –0.38 (–0.48 to –0.29)                                              | Reference           |
| Hypertensive disorders in pregnancy |
| Yes                       | –0.36 (–0.44 to –0.28)                                              | –0.02 (–0.30 to 0.26) |
| No                        | –0.36 (–0.61 to –0.07)                                              | Reference           |
| Mode of delivery          |                                                                     |                     |
| Cesarean                  | –0.23 (–0.39 to –0.08)                                              | –0.17 (–0.34 to 0.01) |
| Vaginal                   | –0.07 (–0.49 to –0.31)                                              | Reference           |
| Maternal educational level|                                                                     |                     |
| Low                       | –0.43 (–0.64 to –0.22)                                              | Reference           |
| Middle                    | –0.35 (–0.46 to –0.24)                                              | 0.08 (–0.15 to 0.32) |
| High                      | –0.30 (–0.46 to –0.14)                                              | 0.13 (–0.14 to 0.39) |
| Highest                   | –0.53 (–0.79 to –0.27)                                              | –0.10 (–0.43 to 0.24) |
| Birth wt, g               |                                                                     |                     |
| Low (< 2500)              | –0.90 (–1.33 to –0.47)                                              | –0.55 (–0.99 to –0.11) |
| Normal (2500-4000)        | –0.35 (–0.44 to –0.25)                                              | Reference           |
| High (> 4000)             | –0.36 (–0.51 to –0.20)                                              | –0.01 (–0.19 to 0.17) |
| Gestational age, wk       |                                                                     |                     |
| Very preterm birth (≤ 33 + 6) | –0.82 (–1.46 to –0.19)                                             | –0.49 (–1.13 to 0.16) |
| Preterm birth (34 + 0 to 36 + 6) | –0.56 (–0.83 to –0.29)                                           | –0.22 (–0.51 to 0.06) |
| Term birth (≥ 37 + 0)     | –0.34 (–0.42 to –0.25)                                              | Reference           |
| Birth wt according to gestational age |
| Small (< –2 SD)           | –0.67 (–1.19; –0.15)                                               | –0.28 (–0.81; 0.25)  |
| Appropriate (± 2 SD)      | –0.39 (–0.48 to –0.30)                                              | Reference           |
| Large (> +2 SD)           | –0.28 (–0.45 to –0.10)                                              | 0.12 (–0.08 to 0.31) |

Abbreviations: GDM, gestational diabetes mellitus.

*Adjusted for maternal age, parity, mode of conception, year of graduation, offspring sex, maternal smoking during pregnancy, maternal nationality, area of residence, cohabiting parents at time of graduation, and maternal educational level.

Table 5. Distribution of high grade point average (≥ 10), grade point average below passing level (< 2) as well as no grade points registered at compulsory school graduation. Given as proportions (%) and odds ratios (OR, 95% CI)

|                      | O-GDM (95% CI) | O-BP (95% CI) | GDM vs No GDM |
|----------------------|---------------|---------------|---------------|
|                      |               |               | Crude         | Model 1      | Model 2 |
| Grade point average ≥ 10 | 276/3777 (7.3%) | 48 639/459 055 (10.6%) | 0.67 (0.59 to 0.75) | 0.55 (0.48 to 0.62) | 0.68 (0.59 to 0.79) |
| Grade point average < 2 | 128/3777 (3.4%) | 11 438/459 055 (2.5%) | 1.37 (1.15 to 1.64) | 1.62 (1.35 to 1.94) | 1.20 (0.96 to 1.50) |
| No grade points registered | 509/4286 (11.9%) | 41 990/501 045 (8.4%) | 1.47 (1.34 to 1.62) | 1.51 (1.37 to 1.66) | 1.38 (1.24 to 1.53) |

Odds were compared using generalized estimating equations to account for correlations within siblings. Model 1 adjusted for maternal age, parity, mode of conception, year of graduation, and offspring sex. Model 2 adjusted for covariates in Model 1 as well as maternal smoking during pregnancy, maternal nationality, area of residence, cohabiting parents at time of graduation, and maternal educational level.

Abbreviations: GDM, gestational diabetes mellitus; O-BP, offspring from background population; O-GDM, offspring of women with gestational diabetes mellitus.
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performance or IQ in adolescents (age > 12 years) or young adults exposed to GDM in utero (18-21, 39).

A Swedish cohort study assessed academic performance in 16-year-olds born during 1973 to 1986. This study included 6390 offspring exposed to diabetes during pregnancy but was not able to segregate GDM from preexisting diabetes mellitus (18). Similar to our findings, this study found that diabetes-exposed offspring were at increased risk of not completing compulsory school and obtaining lower grades. A smaller British study (39) on offspring born during 1991 to 1992 found O-GDM (aged 16; n = 31) to be more likely to obtain low test scores and less likely to obtain high test scores compared to O-BP; however, these results were insignificant. In contrast to our findings, 2 Danish cohort studies found no difference in intelligence (20) and global cognitive scores (21) between offspring exposed to diabetes during pregnancy and O-BP when aged 16 (n = 227) and 18-27 years (n = 153), respectively. The study by Nielsen et al (20) was limited to male offspring and did not differentiate between GDM and preexisting diabetes.

All studies except the study by Nielsen and colleagues (20) adjusted for factors related to socioeconomic status. Hence very few studies have assessed the long-term effect of GDM on academic performance or IQ in adolescents or young adults, and only 2 of these studies were able to differentiate between GDM and preexisting diabetes (21, 39).

### Importance of Academic Performance, Effect Size, and Future Studies

As mentioned earlier, several confounders are significantly associated with GPA. In accordance with previous studies, we found that maternal educational level was the strongest predictor (data not shown), while GDM in this relation was a weaker predictor. The estimated effect size (Cohen’s $D$) of GDM on adjusted GPA was 0.14, which is considered small and unlikely to be of clinical importance on an individual level. In comparison, we estimated the effect size of highest maternal educational level to be 1.14. However, because academic performance in adolescents is correlated

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### Table 6. Maternal, sociodemographic, and offspring characteristics of the study population with no grade point average registered at compulsory school graduation

| Singletons | O-GDM n = 509 | O-BP GDM n = 41990 |
|------------|---------------|---------------------|
| Maternal age, mean (SD), y | 31.1 (5.3) | 28.9 (5.2) |
| Nulliparous, n (%) | 167 (33.1) | 16980 (40.9) |
| Assisted reproductive technologies, n (%) | 16 (3.1) | 554 (1.3) |
| Hypertensive disorders in pregnancy, n (%) | 52 (10.2) | 1652 (3.9) |
| Cesarean delivery, n (%) | 149 (29.3) | 6522 (15.5) |
| Maternal smoking during pregnancy, n (%) | 128 (30.3) | 11830 (33.6) |
| Mother not born in Denmark, n (%) | 113 (22.2) | 6043 (14.4) |
| Area of residence, n (%) | Central and South Zealand 75 (14.7) | 7474 (17.8) |
| Copenhagen and North Zealand 144 (28.3) | 11299 (26.9) |
| Southern of Jutland and Funen 117 (23.0) | 9205 (21.9) |
| Central Jutland 105 (20.6) | 9539 (22.7) |
| North of Jutland 68 (13.4) | 4431 (10.6) |
| Cohabiting parents at time of graduation, n (%) | 294 (57.9) | 23727 (56.6) |
| Maternal educational level n (%) | Low 162 (32.4) | 11006 (26.6) |
| Middle 232 (46.4) | 19108 (46.2) |
| High 81 (16.2) | 7287 (17.6) |
| Highest 25 (5.0) | 3945 (9.5) |
| Birth wt, mean (SD), g | 3573 (694) | 3421 (633) |
| Low birth wt (< 2500), n (%), g | 24 (4.8) | 2624 (6.4) |
| High birth wt (> 4000), n (%), g | 127 (25.0) | 6203 (14.8) |
| Gestational age, mean (SD), d | 270 (15.1) | 277 (15.0) |
| Very preterm birth (< 33 + 6), n (%), wk | 14 (2.8) | 985 (2.4) |
| Preterm birth (34 + 0 to 36 + 6), n (%), wk | 49 (9.7) | 1917 (4.7) |
| Small for gestational age (< –2 SD), n (%) | 16 (4.4) | 1923 (7.2) |
| Large for gestational age (> +2 SD), n (%) | 73 (20.3) | 1149 (4.3) |
| Male sex, n (%) | 319 (62.7) | 26038 (62.0) |
| Cerebral palsy | 17 (3.3) | 1081 (2.6) |

Abbreviations: GDM, gestational diabetes mellitus; O-BP, offspring from background population; O-GDM, offspring of women with gestational diabetes mellitus.
to future education and income (40, 41) the decrease in GPA may be of significant importance at the population level. Adding to this point is the increasing prevalence of GDM. In our study period (1994-2001), 0.85% of Danish pregnancies were affected by GDM. In 2018 the estimated Danish prevalence had increased to approximately 5% (2). Our study was not able to stratify results according to the severity of GDM, and an interesting focus of future studies would be to investigate if the effect of GDM on academic performance is modulated by degrees of glycemic disturbance. Additionally, our finding that the effect of GDM on GPA might be modified by factors such as low birth weight, needs further investigation.

Conclusion

In this Danish national register-based cohort study, we found that 15- to 16-year-old O-GDM had a marginally lower GPA at compulsory school graduation compared to O-BP. The effect was not explained by known confounders or mediators, although low birth weight increased the adverse effect of GDM on GPA. O-GDM were less likely to obtain a high GPA and more likely not to have a GPA registered, while their risk of obtaining a GPA below passing level was similar to O-BP. Overall, differences between O-GDM and O-BP were marginal and unlikely to be of clinical importance.

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