Cognitive function and army-rejection rate in young adult male offspring of women with diabetes: A Danish population-based cohort study

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Running title
IQ at conscript in DM offspring

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Abstract

Objective
While maternal diabetes is a known risk factor for perinatal complications, there is little data on long-term intellectual outcome in offspring. We compare the rejection rate and cognitive functioning of military conscripts according to maternal diabetic status during pregnancy.

Research Design and Methods
We identified a cohort of Danish male offspring of diabetic mothers born between 1976 and 1984 and followed this cohort together with population-based controls to military conscription. The main outcome was army-rejection rate and cognitive function measured with a validated intelligence test.

Results
The army rejection rate was 52.5% among 282 men, whose mothers had diabetes during pregnancy, and 45.4% among 870 controls [risk difference= 7.3 (95% CI: 0.6 to 14.0)]. Mean cognitive scores were 41.4 (95% CI: 40.2 to 42.6) units in diabetes mellitus (DM)-exposed conscripts and 42.7 (95% CI: 42.0 to 43.4) units among controls. Stratification by gestational age, Apgar score, and White class did not change the associations. In a subgroup analysis using available data on glycosylated hemoglobin (A1c) levels during pregnancy, this variable was inversely associated with cognitive functioning. In men with maternal A1c below 7% cognitive score was identical with controls.

Conclusions
The slightly higher army rejection rate in men with maternal diabetes indicates higher morbidity. The identical cognitive functioning in case of well controlled maternal diabetes compared with controls is reassuring, but the negative association between A1c and cognitive score highlights the importance of striving for optimal metabolic control in diabetic women who are or plan to become pregnant.
Background
Maternal diabetes is a risk factor for some perinatal complications that increase the risk of neurological morbidity. (1,2) An altered intrauterine environment, deliveries complicated by a higher prevalence of both preterm and overweight babies, and prolonged stay in intensive care units raise concerns about adequate intellectual development in later life. (3) Previous studies have reported normal development in the first 5-7 years of life of full-term children born to diabetic mothers, but data on outcomes among older children are scarce. (3-5) Silverman et al. conducted a series of intellectual and psychomotor tests in children aged 7 to 11 years in a Chicago cohort originally comprising 196 children born to mothers with type 1 and type 2 diabetes. (6) They found that average scores on a full-scale intelligence test were inversely correlated with maternal A1c levels in the second trimester and with B-hydroxybuturate levels in the third trimester. (7) However, only 94 and 119 children contributed data for the two variables at follow up, making the study vulnerable to selection bias.

Accurate data on cognitive performance in children of diabetic women is important both to mothers and their physicians. If offspring of diabetic mothers show worse cognitive performance than controls, one could attempt to identify modifiable risk factors. Alternatively, documentation of normal intellectual development would be reassuring.

To address this question, we analyzed cognitive function in young men at the time of army conscription according to their mothers’ diabetic status during pregnancy. In a subgroup with data on glycosylated hemoglobin we analyzed the association between this variable and cognitive function. As a fraction of the conscripts is rejected without actual draft examination we also assessed the differences in rejection-rate according to maternal diabetic status during pregnancy.

Material and methods
Setting and study cohorts
From the medical records of obstetrics departments in two Danish hospitals (Rigshospitalet, Copenhagen and Aalborg Hospital, North Jutland County) we formed a consecutive cohort of all boys born between 1976 and 1984 to women with pre-gestational and gestational diabetes (DM-exposed pregnancies). In Denmark all pregnant women are routinely offered regular and free outpatient care and hospitalization if necessary. Care of pregnant diabetic women in eastern Denmark (1.5 m. inhabitants) and North Jutland County (.5 m. inhabitants) is confined to these two departments. Studies on perinatal and neonatal outcomes of diabetic pregnancies in the 1976-1984 period have been published previously. (8,9) For each DM-exposed pregnancy, we identified three control pregnancies from the nationwide Central Office of Civil Registration (CPR Registry) and matched the exposed and the unexposed offspring by birth year and maternal residence at time of birth.

Rejection rate and cognitive score at Draft Board
It is mandatory that all Danish men register with the military Draft Board sometime between the ages of 18 and 20, whereas actual military service may be postponed according to individual preferences, such as according to educational plans. At time of conscription all young men complete a health questionnaire in which they can report chronic health problems that could preclude military service. The Draft Board verifies such reports with health care providers, and men deemed ineligible for military service are exempt from further examination. If the diagnosis is uncertain, draftees are referred to medical specialists for further evaluation. When appropriate, those with severe chronic diseases are excused from the draft at this point. Reasons for exemption are recorded in the Conscript
Registry according to the International Classification of Diseases, 10th revision.(10) Men exempted following input from primary health care providers or medical specialists are not required to present for a medical examination or cognitive testing under the auspices of the Draft Board. Conscription test results are thus unavailable for these men (hereafter referred to as “non-presenters”). To assess the extent of selection bias due to neurological and mental/behavioral conditions among the non-presenters, we constructed a variable comprising ICD-10 codes F (psychiatric and behavioral disorders) and G (diseases of the nervous system) for this group.

The draft suitability of the remaining men (hereafter referred to as “presenters”) is determined by a routine Draft Board evaluation, consisting of a medical examination (with special emphasis on conditions that may interfere with the ability to serve in the military forces) and an intelligence test. All disease conditions detected in presenters are categorized according to the 10th version of the International Classification of Diseases and filed in the Conscript Registry.

All presenters take the Boerge-Prien test, a 45-minute validated group intelligence test developed for the Danish draft board in 1957 and used since then in unmodified form.(11) This 78-item test has four subscales (letter matrices, verbal analogies, number series, and geometric figures). The score equals the total number of correct answers for all 78 questions and is highly correlated with the verbal intelligence quotient (IQ) (0.78), performance IQ (0.71), and full scale IQ (0.82) on the Wechsler adult intelligence scale (WAIS). In a validation study, the mean full scale IQ was 105.8 and the mean Boerge-Prien test score was 44.2.(11)

Following the Draft Board examination, all draftees are categorized as accepted, conditionally accepted, or rejected for military service based on a global assessment of the medical examination and cognitive test results. Evaluation at the Draft Board concerns all branches of the Danish armed services.

We retrieved data on all outcomes for both the DM-exposed and control groups from the Conscript Registry.

Data on pregnancy related covariates

Data on gestational age and Apgar score at five minutes were collected from hospital records and the Danish Medical Birth Registry. The Medical Birth Registry contains information on all births in Denmark since 1 January 1973. Data are obtained from the official reports filed by the midwives who attend all deliveries in Denmark.

For the DM-exposed mothers, we extracted maternal White classification data from hospital records.(12) White class A women are treated with diet only, whereas class B, C, D, and F all represent women with pre-gestational insulin dependency. In addition, we had access to data on maternal glycosylated hemoglobin (A1c) levels for 50 pregnancies in the North Jutland subcohort.

Linkage of data sources

Since 1968 all Danes have received a 10-digit personal registration number at birth or upon immigration. This unique identifier is used in virtually all Danish registries and thus permits unambiguous data linkage.

Statistical analyses

Median and mean values for each outcome category and associations between exposure and cognitive scores were computed with 95% confidence intervals. The Mann-Whitney test was used to compare p-values for medians. We used a significance level of 95%. The distribution of cognitive scores in the DM exposed and control group was displayed graphically with an Epanechinikov kernel density estimation.(13) All analyses using the cognitive score outcome were stratified by week of completed gestation (31st to 38th), two levels of Apgar score (7-10 or below 7), and two levels of White class (A-C and D-
F) in order to test for interaction from these variables. We then fitted an ordinary regression model for cognitive test score as a function of DM exposure and these variables. Because the distribution of cognitive scores was slightly left-skewed, we also repeated the regression analyses using a Box-Cox transformation with estimated lambda=1.5. We also analyzed outcomes for the subgroups of men with scores in the lowest 25th and 10th percentile of the entire Boerge-Prien distribution. In the subgroup from North Jutland with available A1c measurements this variable was analyzed as a continuous variable and displayed in a scatter plot. To assess the potential impact of missing Boerge-Prien scores in non-presenters we conducted sensitivity analyses in which missing values were imputed with scores ranging from 36 to 48 Boerge-Prien units. We used version 9.0SE version of Stata software for all analyses. The study was approved by the Regional Ethics Committee, File No. 2-16-4-5-95.

Results

Descriptive data
Of the 295 young men exposed to maternal diabetes, four (1.4%) died between one month and 17 years of age, six emigrated, one was granted draft deferment, one was rejected from military service due to a criminal sentence, and one was lost to follow-up, leaving 282 (96%) men born to 259 mothers with information about acceptance or rejection for military service. The control group consisted of 870 young men with this information.

Rejection for military service
In the DM exposed group 54 (19.2%) were rejected as non-presenters compared with 134 (15.4%) among controls (risk difference (RD) = 3.8%; 95% CI: -1.4 to 8.9). The prevalence of rejection due to diagnoses from ICD-10 category F and G was 6.0% and 5.2%, respectively (RD = 0.8%; 95% CI: -13.8 to 13.0). When presenters and non-presenters were combined, the rejection rate was 52.5% (148/282) among DM exposed compared with 45.4% (395/870) among controls (RD = 7.3% (95% CI: 0.6 to 14.0). The medical reasons for rejection among both non-presenters and presenters were evenly distributed among the other ICD-10 categories without predominance of diagnoses that could be related to cognitive performance (data not shown).

Cognitive scores
Boerge-Prien scores were available for 227 DM exposed conscripts and 736 controls. Median scores were 43 units (interquartile range 36 to 48 units in DM exposed and 37 to 49 units in controls) in both groups (p=0.12). Mean values were 41.4 units (95% CI: 40.2 to 42.6) in DM exposed and 42.7 units (95% CI: 42.0 to 43.4) in controls. This difference of 1.27 units (95% CI: -2.70 to 0.14) equals 3.0 points on the commonly used IQ scale. Estimates from analyses stratified for gestational week, categories of 5-minute Apgar scores, and maternal White class were virtually identical to the crude estimates. Because inclusion of these three variables in the regression model did not change the estimates, we report results from the crude analysis only. The results after the Box-Cox transformation of cognitive scores were consistent with the findings from the regression analysis with the untransformed Boerge-Prien scores (data not shown). Figure 1 shows the densities of cognitive scores in the two groups estimated with an Epanechnikov kernel density. In the subgroups with cognitive scores in the lowest 25th (n=241) and 10th (n=97) percentiles, the estimates were also identical with the crude analysis (data not shown). The associations remained virtually unchanged when the analyses were repeated in a sub-cohort where each woman contributed only with her first recorded pregnancy.
In the sensitivity analyses with imputed Boerge-Prien scores in the 189 cases without available data we re-calculated the estimated difference in scores in the two groups by each imputation level. With an imputation level of 39 units the difference was -1.18 (95% CI: -2.36 to 0.01) and the association became gradually more negative for all lower imputed values.

In the subgroup of 39 pregnancies with available data on both A1c and cognitive score we found that one percentage-point increase in A1c value was associated with a 2.6-point decrease in the cognitive score (95% CI: 1.8 to 4.8). In 19 pregnancies with A1c values ≤7.0% the mean cognitive score was 42.6 units whereas the score was 39.1 units in 20 pregnancies with A1c >7.0% equivalent to a difference of 3.5 units (95% CI: 0.6 to 7.9) compared with controls. Figure 2 depicts the association between A1c and cognitive score together with a Box-and-whisker plot of the scores among controls and DM exposed without A1c values.

Discussion
To our knowledge this is the largest cohort study to date of the cognitive consequences of exposure to maternal diabetes, with the longest and most complete follow-up. The DM-exposed cohort constitutes a population-based consecutive sample, with almost complete follow-up into young adulthood. We also procured a concurrent, population-based control group. Evaluation by the Draft Board is mandatory for all Danish men.

When presenters and non-presenters were considered together, the rate of rejection for military service was higher in the DM-exposed group. Among presenters there was only a small decrease in cognitive score associated with DM-exposure. In the subgroup with available data on glycosylated hemoglobin, we found a significant negative association between maternal A1c level and cognitive score adjusted for other perinatal risk factors. However, the cognitive scores in men exposed to A1c below 7% were identical with the figures observed among controls. Several potential study weaknesses deserve discussion. Differences in reasons for rejection in non-presenters could introduce selection bias. However, our observation of identical proportions of rejection due to neurological and mental/behavioral conditions in both presenters and non-presenters decreases this concern. And in the sensitivity analyses the association remained stable throughout a wide range of imputed cognitive scores indicating that the observed association is fairly robust. Data entry errors are another possible source of bias, but all data were collected prospectively without knowledge of maternal exposure status, and such errors are likely to be non-differential. They would lead to underestimation of the true associations. Another concern is that some draftees intentionally may have performed worse on the test than would be expected according to their actual IQ level in order to avoid military service. However, we find it unlikely that such behaviour would depend on maternal diabetic status during pregnancy. Likewise we find it unlikely that deterioration of maternal disease status with subsequent need for additional care at time of conscription would seriously affect the performance of a son at conscription. In Denmark patients with chronic conditions, like blindness, receive supplementary benefits, and arrangements for private care of diseased or disabled family members are therefore rare.

Registry data lack information about several factors that could confound the observed association if they were unevenly distributed by maternal diabetes status. Examples include maternal smoking and duration of breastfeeding, which previously have been shown to be associated with cognitive performance.(15,16) However, available research findings indicate that parental socioeconomic factors only partially mediate the association between restricted fetal growth and low intellectual
The observation of identical cognitive scores in young adulthood in offspring of diabetic women with A1c below 7% and controls is reassuring for diabetic women who plan to become pregnant. But the observed negative association between metabolic control and adult cognitive functioning adds further evidence to the importance of striving for optimal metabolic control during pregnancy.\(^{(18-20)}\)

The higher morbidity among sons of diabetic mothers accords with a nationwide Swedish registry based study reporting a slight increase in the number of hospitalizations in children born to mothers with diabetes compared with population based controls.\(^{(21)}\) The reasons for these observations and the pattern in the excess morbidity deserve more detailed analyses.

In a cohort of 282 Danish men aged 18-20 years born to diabetic mothers, we found a slightly higher army-rejection rate compared with population controls. A minor difference in intellectual performance was found between the two groups, but subgroup analyses indicate that the difference may be confined solely to women with suboptimal metabolic control during pregnancy.

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The researchers conducted their research independently from their funding sources in all respects.

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Reference List

13. *Stata Statistical Software*. College Station TX, United States, StataCorp LP, 2006

Figure 1  Distribution of Boerge-Prien scores for DM exposed and control groups using Epanechnikov kernel density estimation

Legend:
Full line = DM exposed, dashed line = controls
Figure 2  Box-and-whisker plot of Boerge-Prien scores for controls; DM exposed without A1c values; and the association between A1c and Boerge-Prien score in 39 DM exposed with A1c values

Legend:
Left side panel: Scatter plot with regression line of A1c versus cognitive score in 39 DM exposed with A1c values. Shaded area represents 95% confidence band. X-axis label represents A1c values from 4.0 to 10.0%.

Right side panel: Controls (n=736) and DM exposed without A1c values (n=189). The middle lines mark the median, the top and bottom of the boxes mark 75\textsuperscript{th} and 25\textsuperscript{th} quartiles, the whiskers extends from the quartiles to observations no farther than 1.5 times the interquartile range. More extreme observations are plotted individually.