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Manuscript title: Prenatal exposure to fever and infections and academic performance. A multilevel analysis.

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Abbreviations:
Estimated pupil ability: EPA
Odds ratio: OR

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Abstract: Prenatal exposure to fever and infections has been linked to various neurodevelopmental disorders, but it is not yet known whether more subtle effects on neurodevelopment may exist as well. The aim of this study was therefore to investigate whether these early life exposures were associated with academic performance in childhood and early adolescence. Children and mothers who were enrolled in the Danish National Birth Cohort during 1996-2002 were included in this study. Information on fever and common infections in pregnancy was prospectively collected in two pregnancy interviews and linked with assessments of academic performance from the Danish National Tests in 2010-2013. Hierarchical multilevel linear regression of 216,350 assessments in 71,850 children born to 67,528 mothers revealed no differences in academic performance in children, according to prenatal exposure status for fever (OR=1.01, 95% CI: 1.00, 1.03), any infection (OR=1.00, 95% CI: 0.99, 1.01), genitourinary infections (OR=1.01, 95% CI: 0.99, 1.02), prolonged cough (OR=1.00, 95% CI: 0.99, 1.02) and diarrhea (OR=0.99, 95% CI: 0.97, 1.00). The findings were supported in different types of academic assessments, different timings of exposure, and in sibling comparisons. This large population-based study suggests that prenatal exposure to fever and common infections does not affect the child's basic school performance.

Keywords: Fever**,** Infection, Maternal exposure, Neurodevelopmental disorders, Cohort Studies, Multilevel analysis, Matched-Pair Analysis

Introduction

Prenatal exposure to fever and infection has been linked to adverse neurodevelopmental outcomes in offspring, such as autism, schizophrenia, cerebral palsy, and intellectual disability(1-3). When an expectant mother experiences a fever or infection, cytokine levels in the fetal environment can change and cause cellular processes in the fetal brain to become altered or dysfunctional. Such changes may ultimately cause long-term neurodevelopmental deficits in the child(4). Existing studies concerning the neurodevelopmental impact of prenatal exposure to fever and infection have primarily focused on diagnosed disorders. Little is known about whether more subtle adverse effects on cognitive abilities may be associated with these exposures as well.

Poor academic performance may result from impaired cognition, and is associated with substantial societal costs in terms of additional educational expenses, loss of intellectual contribution to society as well as diminished economic productivity (5, 6). Fever and infections occur in approximately 25% and 60% of pregnancies, respectively (7, 8). Given the high proportion of exposed pregnancies, even a small negative effect at the individual level may have a substantial societal impact and cause a shift in the overall distribution of academic performance (9). It is well known that maternal infection during pregnancy with some TORCH-infections, such as *toxoplasmosis gondii*, *rubella*, *cytomegalovirus*, and *herpes simplex virus* are associated with adverse neurodevelopmental outcomes in the child, such as learning disabilities and cognitive delay (10). In addition, hospital recorded maternal infections have recently been linked to a decrease in general cognitive ability in a Danish nationwide register study of 161,696 young men (11). However, it is not yet known whether prenatal exposure to fever and less severe infections, such as urinary tract-, respiratory tract- and gastric infections may also affect cognitive abilities and academic performance. One ecological study of 182,913 Norwegian conscripts, indicated reduced mean intelligence in adulthood among men born during the year following an outbreak of the Hong Kong flu (12). An association between fever in the second trimester of pregnancy and academic performance has likewise been reported in a study of 6,388 children comprising the Helsinki Longitudinal Project (13, 14), but further research is needed to validate these findings.

Academic performance is affected by an array of genetic, environmental and social influences, and isolating these effects from one another can be methodologically challenging. When important influences are left unobserved or uncontrolled for, this can lead to biased exposure estimates. With these challenges in mind, we aimed to investigate whether prenatal exposure to fever and common infections affected academic performance in children.

Methods

Study population

This study was conducted within the Danish National Birth Cohort, which is a nationwide cohort of pregnant women and their offspring (15). During 1996-2002 pregnant women were recruited from their general practitioners, when they attended the first antenatal visit. The women were invited to complete two computer-assisted telephone interviews at approximately gestational week 12 and 30 covering a range of lifestyle and health-related questions. Criteria for inclusion in the cohort were intention to carry the pregnancy to term, residence in Denmark, and sufficient language skills to participate in telephone interviews. Written informed consent was obtained from all cohort participants before entering the study and this study has been approved by the Danish Data Protection Agency (journal number: 2013-41-1431).

Academic performance

Academic performance in the children was measured using IT-based assessments from the Danish National Test Program (16). The program was introduced in 2010 and is mandatory for all public primary and lower secondary schools, covering approximately 85% of all children living in Denmark. Linkage using the child's personal identification number allowed us to access all available assessments from children in the cohort in the years 2010-2013. Estimates for language performance was available in 2nd, 4th, 6th and 8th grade, covering three profile areas (language comprehension, decoding, and reading comprehension) and for mathematical performance in 3rd and 6th grade, also covering three profile areas (numbers and algebra, geometry and applied mathematics). The assessments were developed based on a Rasch model (17), and provides an adaptive measure of cognitive ability, called the estimated pupil ability (EPA). The EPA is reported on a log scale ranging from -7 to 7 with higher scores indicating higher ability. For the analyses presented in this study the average EPA across the three profile areas was summarized, to constitute one combined score for each assessment (language in 2nd, 4th, 6th and 8th grade and math in 3rd and 6th grade, respectively).

Measures of fever and infection exposure

Exposure to fever and infections in pregnancy was assessed using self-reported data from the two pregnancy interviews. The women were asked whether they during this pregnancy had experienced episodes of fever and a range of common infections. Specific infections included genitourinary infections (cystitis, pyelonephritis, and vaginal symptoms), prolonged cough, and diarrhea. Timing of fever episodes was divided into ten four-week periods (gestational weeks 1-4, 5-8, 9-12, …,, 37-40), with binary variables indicating exposure status for each period (yes/no). Information on duration and severity of the fever episodes was furthermore available (18, 19).

Confounder adjustment

Selection of potential confounders was based on existing evidence. Information on maternal age at birth was extracted from the Danish National Patient Register (20) and season and year of birth was obtained from the Danish Medical Birth Registry (21). For maternal educational attainment we used the highest level of completed education listed in the Population's Education Register (22). If the mother was enrolled at an educational institution at the time of giving birth we used the highest level of ongoing education. Maternal smoking status at the time of the interview (yes/no) and number of children in the household (none, 1, ≥2) was extracted from the first pregnancy interview, whereas maternal stress in pregnancy was obtained from the second. Maternal stress was based on nine questions concerning potentially stressful conditions during pregnancy (e.g. living conditions, finances, health, work, relationship), and was categorized as high (the mother reported having been burdened a lot by two or more conditions), medium (burdened a lot by one condition), or low (not burdened a lot by any condition). In addition, in order to distinguish between fever and infections, we adjusted all analyses concerning fever for infections and vice versa.

Statistical analyses

Several assessments of academic performance were available for the majority of the children included in the study. Given that some of the children furthermore had siblings that were also part of the cohort the assessments were not statistically independent from each other. Ignoring such dependency would lead to underestimation of standard errors and accordingly inflate the risk of type one errors. Hierarchical multilevel linear regression with three levels was consequently applied, where the assessments were considered as being nested within children and the children as being nested within mothers.

Academic performance, measured by the EPA value, Y_{ct} for child c at time t was analyzed using the model

$$Y_{ct} = A_c + B_m + d_{ct} + E_{ct}$$

where A_c and B_m are random effects for child, c, and mother, m, respectively, d_{ct} is the mean value and E_{ct} the residual. The mean value is linear in the predictor variables which include information on fever and infections as well as subject and the potential confounders. Separate models were specified for fever and timing of fever as well as for the different infections. As we were mainly interested in the exposure estimates, we specified all models using maximum likelihood estimation, as this approach is argued to provide the most accurate estimates of the fixed effects (23). Intercept-only models were used to estimate the intraclass correlation coefficient, in order to assess the amount of correlation of assessments within children and siblings.

Since the EPA values are Rasch scores on a log scale, regression coefficients β for variables in the mean value d_{ct} can be interpreted as log(odds ratios) for answering a given test question correctly. Thus, the coefficient β for fever has the interpretation that exp(β) is the ratio between the odds (OR) of answering a given question correctly between children exposed or unexposed for fever for any given values of the other explanatory variables. For ease of interpretation we have presented all estimates as ORs and their corresponding 95% confidence intervals.

Sensitivity analyses

To address issues of potential uncontrolled and residual confounding in the multilevel models we used a sibling discordance approach, in a subsample of sibling pairs within the cohort. By analyzing outcome differences in exposure-discordant siblings we essentially matched on fixed family characteristics, allowing us, by design, for adjustment of important potential confounders such as maternal cognitive ability and socioeconomic status and some adjustment for variables that were non-stable, but correlated in postnatal life of siblings (24, 25). To enhance comparability within siblings, we restricted these analyses to pairs, where similar assessments were available. Specifically, we considered language assessments in 4th grade and mathematical assessments in 3rd grade, as these assessments were most frequently represented. We conducted matched analyses of exposure discordant siblings using paired t-tests to estimate mean differences in EPAs for language and math assessments, respectively.

To account for missing information on academic performance we used inversed probability weighting (26) in a sensitivity analysis to assess whether our results were biased from non-participation. By using inversed probability weights each assessment was given a weight proportional to the inverse probability that it was observed (i.e. not missing), given the specified covariates. The weighted analyses consequently provided an estimate of the association between prenatal fever/infection and academic performance, in the scenario where no assessments of academic performance were missing. The weights were based on a logistic regression model and included, in addition to the exposure variables and covariates from the analysis model, child contact to the psychiatric system (yes/no), maternal income in the year prior to birth (quintiles), and birth weight (gram). Since it is not possible to include such weights in the multilevel models in standard software, this sensitivity analysis was performed in two steps. First, we reanalyzed the data using a standard multiple linear regression model (disregarding possible dependencies in the data). Since this resulted in virtually unchanged estimates (albeit with more narrow confidence limits) we, next, included the weights in this standard model.

All analyses were performed using Stata (StataCorp, College Station,Texas).

Results

A total of 216,350 assessments were available for 71,850 children born to 67,528 mothers. The median number of assessments per child was 3.0 (range 1-5). Figure 1 illustrates the process of inclusion into the study.

INSERT FIGURE 1

Descriptive analysis

Prenatal fever exposure was reported in 19,982 (27.8 %) of the children included in the study, while 43,208 (60.1%) of the children were exposed to infections. Genitourinary infections, diarrhea and prolonged cough were all frequently reported, with respectively 25.2%, 22.7% and 15.1% of pregnancies being affected. Maternal-, birth-, and child- characteristics of the study population according to fever and infection exposure are shown in Table 1. Women who reported fever and infections tended to be better educated, to be more likely to smoke, to be stressed, to have more children in the household, and to have given birth in April-September, compared to unexposed women. No substantial difference according to maternal age and calendar year of birth was observed.

18,657 (20.1%) children were excluded due to a lack of assessment of academic performance. Mothers of children without assessments were more likely to have higher education, to have given birth in the end of the recruitment period and to have given birth in January to March compared to mothers of children for whom assessments were available. In the group of excluded children, there were also a higher proportion of boys compared to girls.

INSERT TABLE 1

Characteristics of the assessments of academic performance according to subject, grade, test year, and gender are available in Table 2. Overall, the mean EPA was 1.09 (standard deviation=1.05), with language assessments generally being higher (mean= 1.37, standard deviation=1.08), compared to math assessments (mean=0.65, standard deviation=0.84). While language scores seemed to increase somewhat over the years of testing, the opposite trend was observed for math assessments. Girls tended to perform better in the language assessments, while boys achieved slightly higher scores in math.

INSERT TABLE 2

Multilevel analysis

Table 3 presents the hierarchical multilevel linear regression analyses of the association between prenatal exposure to fever and common infections and academic performance. The intraclass correlation values show that assessments of academic performance are moderately correlated both within individuals and within siblings. The analyses show that neither fever nor common infections in pregnancy is associated with academic performance in primary and lower secondary school, with ORs ranging from 0.99 to 1.01. Thus, for two children who are similar on all other explanatory variables, the child that is prenatally exposed to fever or infection has the same odds of answering any given question correctly as the unexposed child. Excluding TORCH infections from the analyses considering any infection did not change the estimate (data not shown). Only fever had a negligible, positive association in the adjusted analyses (OR= 1.01, 95% CI: 1.00-1.03). When we considered fever exposure in the different gestational periods none were associated with lower scores, and only fever in weeks 1-4 were associated with a somewhat higher score (OR: 1.05, 95% CI: 1.01-1.11), see Web Table 1. In Web Table 2 additional analyses are presented separately for language and mathematical performance and for each profile area. These findings are in line with those presented in Table 3 with the exception that diarrhea seemed to have a minor negative association with mathematical performance.

INSERT TABLE 3

Sensitivity analysis

Academic performance was additionally compared in a subsample of sibling pairs within the Danish National Birth Cohort. 4th grade language and 3rd grade math assessments were available for 2,781 and 1,222 pairs of siblings, respectively. Only pairs that were discordant in prenatal exposure to fever and infections contributed to each analysis, see Table 4. Consistent with the multilevel analysis, no differences in academic performance were observed in the within-sibling comparisons.

INSERT TABLE 4

In order to ascertain the effect of the children that were excluded due to missing assessments of academic performance, we additionally conducted analyses using inversed probability weighting. The weighted analyses were essentially identical to the unweighted analyses, suggesting that missing data did not bias the estimates (data not shown).

Discussion

In this study, we found no evidence to suggest that prenatal exposure to fever and common infections have any measurable impact on academic performance in childhood and early adolescence. Neither multilevel analyses of more than 200,000 assessments of academic performance in more than 70,000 children nor the sibling discordance analyses, which may control for confounding more effectively, showed any impact of these early-life exposures, as initially hypothesized. However, prenatal fever exposure showed a minor positive association with academic performance in the multilevel analysis, suggesting that children that were prenatally exposed to fever had slightly better academic performance compared to children that were unexposed. Given the unexpected direction of the association, we do however suggest that this estimate is interpreted with caution. One potential explanation might be, that some maternal characteristics that affect the child's academic performance, such as intelligence, also is associated with recall of fever. The association between fever and academic performance was not replicated in the sibling comparisons, supporting that it may be explained by insufficient adjustment of confounding in the multilevel analyses or perhaps a simple chance finding.

This lack of an association is not consistent with some of the previously published literature. In the ecological study by Eriksen and colleagues (12), they hypothesized that reduced mean intelligence in a large sample of Norwegian conscripts was possibly explained by prenatal exposure to influenza. These differing findings may be explained by differences in the study design. The Norwegian study considered aggregate data on exposure and outcome whereas this study used individual-level information. Ecological studies are limited in their ability to infer causality, as aggregate level correlations may exist even in the absence of an individual-level correlation (ecological fallacy). The analyses presented in this publication are however restricted to infections that were directly addressed in the interviews in the Danish National Birth Cohort. It cannot be ruled out that some common infections that are not considered specifically, such as influenza, may be adversely associated with academic performance in this sample as well.

In the register-based study from Denmark maternal infections during pregnancy was furthermore associated with impaired cognitive ability (11). The study considered only infections that required hospitalization, which possibly indicates that while prenatal exposure to severe infections may harm the child's cognition this may not apply to common infections resulting only in mild illness.

In another study by Dombrowski and colleagues fever during the second trimester of pregnancy was found to be associated with impaired academic performance at age 12 (13, 14). They argued that the harmful effect of fever was restricted to specific vulnerable periods of the pregnancy. To examine whether such time-dependent association was present in our sample, we also considered fever during different gestational periods. Academic performance was however, not impaired following fever at any time of pregnancy. In line with our findings, no differences in IQ scores among children that were prenatally exposed to high fevers and their unexposed counterparts, were reported in an American study (27).

Infections have frequently been cited as a possible explanation of a seasonality effect observed in many studies on neurodevelopmental outcomes(28). Such effect of season of birth in academic performance was also observed in this study. However, the multilevel models revealed that prenatal infections and fevers did not account for this pattern. Instead, differences in age caused by school entry during the summer, might explain why children born in the fall tended to have inferior academic performance compared to children born in spring.

Major strengths of the current study are the prospective assessment of exposure information, which occurred many years prior to assessments of academic performance. Missing information and flawed recall is therefore expected to be independent from the assessment of the child’s academic performance, minimizing the risk of information bias. In addition, given the large sample size we were able to exclude that even very subtle differences in academic performance existed, since 95% confidence limits did not exceed ±0.03 for fever or any of the infections.

The validity of the findings relies on the measures used to assess academic performance in the children. The assessments that are part of the National Test Program are argued to provide an objective measure of student ability, due to the absence of teacher evaluation in the grading. The adaptive nature of the assessments has furthermore been shown to provide a more accurate estimate of a student’s ability level, as opposed to regular linear tests (16). Nevertheless, the reliability of the assessments has been widely discussed in the public debate (29). For the purpose of this study, however, we used several measurements in different time periods, making the findings more robust towards the uncertainty of single measurements. Also, it may be of interest to distinguish between children that scored within a normal range on the test, and children that did not. However, given that the tests have only recently been introduced, there is no lower cutoff with an established clinical meaning. Furthermore, dichotomizing a quantitative outcome will inevitably lead to a loss of information.

Special consideration should be given if academic performance is perceived as a proxy for cognitive function. Cognitive function and academic performance have been shown to correlate highly (30), but academic performance depends on various other factors as well. Based on the analyses presented in this publication it is therefore important to note, that it is not possible to assess whether cognitive function may in fact be affected by prenatal exposure to fever and infections. The analyses do however show that if such association exists it does not have any measureable effect on the academic performance of those children in childhood and early adolescence.

The sibling discordance comparisons provided an effective mean of controlling for unmeasured confounders, such as parental intelligence(31). The findings from these sensitivity analyses were in accordance with the multilevel analyses, indicating that unmeasured or residual confounding did not bias the results of the multilevel analyses. In the sibling comparisons one might, however, be concerned about potential bias from birth order, as birth order is associated with the child's risk of exposure (see Table 1) as well as academic performance in our sample. However, given that younger siblings were more likely to be prenatally exposed to fever and infections, and also more likely to perform worse on the tests than their older sibling, we would expect that such bias would mimic a harmful effect of fever/infections. Since none of the sibling analyses indicated any association between fever/infections and academic performance, the magnitude of such bias is most likely modest and a correction would lead the estimates towards null, and thus reinforcing the conclusions as already made.

Approximately 1 in 5 children of the Danish National Birth Cohort were excluded from the analyses, primarily due to the lack of assessments of academic performance. Differences between children with and without assessments were observed in terms of the mother's educational attainment, year of birth and gender. Several mechanisms are likely to account for this selection. Firstly, many children attending private schools were not subject to testing, which may explain why mothers of children with no assessment tended to have higher educational attainment. Secondly, differences in year of birth are most likely explained by the younger cohorts not having reached the appropriate grade for testing yet. Lastly, exemption for various reasons have been reported in around 2-3% of all children at the national level (32), and is more frequent among boys compared to girls (33). One potential concern was that children from the lower end of the ability distribution were more likely to be exempt from the tests (33). However, when we accounted for missingness by applying inverse probability weights, the results remained essentially unchanged, suggesting that our findings were not biased by this selection.

In summary, our findings are reassuring for women experiencing fevers and common infections in their pregnancy, as we consistently found that such prenatal exposures were unrelated to academic performance in childhood and early adolescence.

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Table 1: Characteristics of the Study Population According to Exposure Status, Denmark, 1997-2003

	Total	Fever		Infection		No test results
		No	Yes	No	Yes	
Characteristic	N = 71,850	N = 51,730	N = 19,982	N = 24,198	N = 43,208	N = 18,657
	%	%	%	%	%	%
Age at birth (years)						
≤24 years	13.1	13.3	12.8	13.5	12.6	12.1
25-29 years	41.9	42.0	41.8	43.3	41.4	40.1
30-34 years	33.9	33.5	34.8	33.0	34.5	34.5
≥ 35 years	11.1	11.3	10.6	10.2	11.5	13.3
Education						
Primary education	11.4	11.4	11.4	10.8	11.4	10.8
Secondary education	43.7	44.5	41.4	45.2	43.1	38.7
Higher education	44.7	43.9	47.0	43.9	45.4	50.1
Missing	0.2	0.2	0.2	0.1	0.2	0.4
Smoking						
No	70.6	70.9	70.0	72.1	70.0	72.3
Yes	25.4	24.8	27.0	23.4	26.0	23.2
Missing	4.1	4.3	3.0	4.5	4.0	4.6
Stress						
Low	69.3	70.8	65.6	79.3	69.9	66.9
Medium	16.2	15.2	19.0	14.8	18.5	16.0
High	8.3	7.1	11.5	5.9	10.4	8.5
Missing	6.2	7.0	3.9	0.0	1.3	8.6
Children in household						
0	43.5	45.5	38.5	48.1	40.4	46.6
1	36.6	34.8	41.7	32.8	39.1	34.0
≥2	15.8	15.4	16.7	14.7	16.4	14.9
Missing	4.1	4.3	3.1	4.5	4.0	4.5
Calendar year						
1997-1999	35.9	35.6	36.8	34.6	37.6	25.0
2000-2001	46.5	46.1	47.6	47.6	44.9	30.8
2002-2003	17.6	18.3	15.7	17.8	17.5	44.2
Birth month						
January-March	23.1	24.6	19.0	22.4	23.2	32.1
April-June	25.8	24.0	30.3	22.8	27.4	21.7
July-September	27.7	26.2	31.9	28.6	27.6	21.9
October-December	23.5	25.2	18.8	26.3	21.8	24.3
Gender						
Boy	50.3	50.3	50.3	50.6	50.1	54.5
Girl	49.6	49.6	49.6	49.3	49.9	45.3
Missing	0.1	0.1	0.1	0.1	0.1	0.2

Table 2: Characteristics of assessments (mean scores and standard deviations, SD) according to subject, grade, test year, and gender. 2010-2013, children from the Danish National Birth Cohort.

	Overall		Language		Mathematics	
Characteristic	*n*	*Mean score (SD)*	*n*	*Mean score (SD)*	*n*	*Mean score (SD)*
Overall	216,350	1.09 (1.05)	133,186	1.37 (1.08)	83,164	0.65 (0.84)
Grade						
2nd	28,226	1.35 (1.27)	28,226	1.35 (1.27)		
3rd	44,781	0.83 (0.84)			44,781	0.83 (0.84)
4th	59,478	1.18 (1.00)	59,478	1.18 (1.00)		
6th	76,853	0.95 (1.01)	38,470	1.46 (0.95)	38,383	0.44 (0.78)
8th	7,012	2.48 (0.91)	7,012	2.48 (0.91)		
Test year						
2010	42,865	1.06 (1.07)	27,619	1.19 (1.16)	15,246	0.82 (0.83)
2011	61,199	1.10 (1.03)	38,199	1.34 (1.07)	23,000	0.71 (0.83)
2012	59,421	0.97 (0.98)	30,516	1.30 (1.00)	28,905	0.63 (0.83)
2013	52,865	1.23 (1.13)	36,852	1.57 (1.07)	16,013	0.43 (0.83)
Gender						
Boy	108,717	1.03 (1.08)	66,810	1.26 (1.13)	41,907	0.67 (0.88)
Girl	107,480	1.15 (1.03)	66,280	1.47 (1.02)	41,200	0.63 (0.79)

[a]SD: Standard deviation

Table 3: Crude and adjusted effects from hierarchical multilevel linear regression analyses of maternal fever and infection on academic performance presented as odds ratios (ORs). 2010-2013, children from the Danish National Birth Cohort.

	Academic performance					
	Overall sample: $n_{assesments}$ =216,350, $n_{children}$ =71,850, $n_{mothers}$ = 67,528					
Prenatal exposure	Assessments *n*	crude OR	95% CI	Assessments *n*	adjusted OR[b]	95% CI
Fever	215,951	1.00	0.99, 1.02	192,728	1.01	1.00, 1.03[c]
Any Infection	203,201	1.00	0.99, 1.02	192,728	1.00	0.99, 1.01
Genitourinary infection	201,112	1.01	0.99, 1.02	192,234	1.01	0.99, 1.02
Prolonged cough	202,920	0.99	0.97, 1.00	193,968	1.00	0.99, 1.02
Diarrhea	216,124	0.99	0.98, 1.01	194,165	0.99	0.97, 1.00

Abbreviations: OR, Odds ratio.

[a] Intraclass correlation coefficient for level 3 (mother): 0.255, ICC for level 2|level 3 (child|mother): 0.4388

[b] Models are adjusted for maternal age, maternal education, maternal smoking, maternal stress, number of children in the household, calendar year of birth, birth month and subject/grade. Analyses considering fever are furthermore adjusted for the effect of infections, and the analyses on infections are adjusted for the effect of fever.

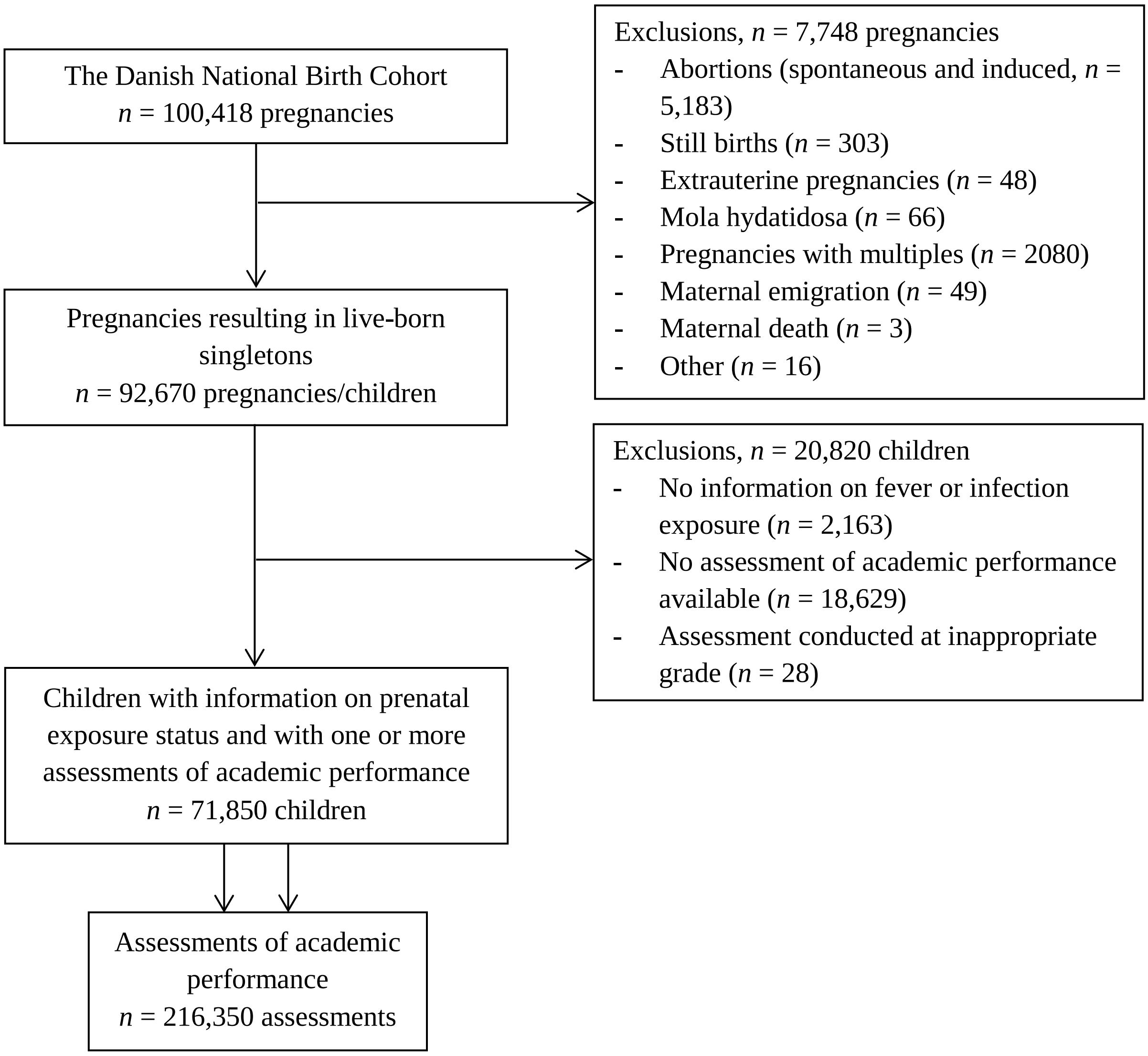
[c] P-value< 0.05

Table 4: Mean EPA difference in pairs of exposure discordant siblings within the Danish National Birth Cohort (2010-2013).

	Language 4th grade *n = 2,781 pairs*			Mathematics 3rd grade *n = 1,222 pairs*		
Prenatal exposure	*Discordant pairs n*	*Mean difference*	*95% CI*	*Discordant pairs n*	*Mean difference*	*95% CI*
Fever	906	-0.06	-0.13, 0.01	385	0.08	-0.03, 0.19
Infection	977	0.04	-0.03, 0.11	444	0.03	-0.07, 0.12
Genitourinary infections	787	0.05	-0.03, 0.12	331	-0.02	-0.13, 0.09
Prolonged cough	634	-0.04	-0.13, 0.05	256	0.09	-0.04, 0.22
Diarrhea	836	0.01	-0.06, 0.09	360	0.06	-0.05, 0.17

Abbreviations: EPA, Estimated Pupil Ability.

Figure 1: Flow chart of study population and assessments of academic performance



Web Table 1: Adjusted estimates of the association between timing of maternal fever and academic performance in the child. Hierarchical multilevel linear regression analyses, with estimates presented as odds ratios. 2010-2013, children from the Danish National Birth Cohort.

	Academic performance		
	Overall sample: $n_{assesments}$ *=190 402,* $n_{children}$ *=63 109,* $n_{mothers}$ *= 59 689*		
Gestational week	Assessments *n*	adjusted OR[b]	95% CI
1-4	190,402	1.05	1.01, 1.11[c]
5-8	190,402	1.02	0.99, 1.05
9-12	190,395	1.02	0.99, 1.05
13-16	190,383	1.01	0.98, 1.04
17-20	190,363	1.00	0.96, 1.03
21-24	190,109	1.03	0.00, 1.07
25-28	181,142	1.00	0.97, 1.04
29-32	95,105	1.01	0.96, 1.05
33-36	24,298	1.06	0.97, 1.15
37-40	560	0.93	0.52, 1.69

Abbreviations: OR, Odds ratio.

[a] The analysis of each time-interval is only based on pregnancies where we have full information on all four weeks. I.e. if a woman had her last interview in gestational week 27, then the child contributes to the analyses up until gestational week 24. The child is not included in the analyses of week 25-28 (incomplete data) or the remaining 3 time-periods (missing data).

[b] The model is adjusted for maternal age, maternal education, maternal smoking, maternal stress, number of children in the household, calendar year of birth, birth month, subject/grade, and infections.

[c] P-value< 0.05

Web Table 2: Crude and adjusted effects from hierarchical multilevel linear regression analyses of maternal fever and infection on cognitive ability according to subject and subscale, presented as odds ratios. 2010-2013, children from the Danish National Birth Cohort.

	Language					**Mathematics**				
	$n_{assesments}$ = 133,186, $n_{children}$ = 71,399, $n_{mothers}$ = 67,105					$n_{assesments}$ = 83,164, $n_{children}$ = 69,191, $n_{mothers}$ = 65,095				
	Overall	*Overall*	*Language comprehension*	*Decoding*	*Reading comprehension*	*Overall*	*Overall*	*Numbers and algebra*	*Geometry*	*Applied math*
Prenatal exposure	crude OR (95% CI)	adjusted OR[a] (95% CI)				crude OR (95% CI)	adjusted OR[a] (95% CI)			
Fever	1.01 (0.99, 1.02)	1.02 (1.00, 1.03)[b]	1.02 (1.00, 1.03)[b]	1.01 (0.99, 1.03)	1.02 (1.00, 1.04)[b]	1.00 (0.98, 1.01)	1.01 (1.00, 1.02)	1.00 (0.99, 1.02)	1.01 (0.99, 1.02)	1.02 (1.00, 1.03)
Any Infection	1.01 (0.99, 1.03)	1.00 (0.99, 1.02)	1.01 (1.00, 1.02)	0.99 (0.97, 1.01)	1.00 (0.98, 1.02)	0.99 (0.97, 1.00)[b]	1.00 (0.99, 1.01)	1.00 (0.99, 1.02)	1.00 (0.99, 1.01)	1.00 (0.98, 1.01)
Genitourinary infection	1.01 (0.99, 1.03)	1.02 (1.00, 1.03)	1.02 (1.00, 1.03)[b]	1.02 (0.99, 1.04)	1.02 (1.00, 1.04)[b]	1.00 (0.99, 1.02)	0.99 (0.98, 1.01)	0.99 (0.98, 1.01)	1.00 (0.98, 1.01)	1.00 (0.98, 1.01)
Prolonged cough	0.98 (0.95, 1.00)[b]	0.99 (0.97, 1.01)	1.00 (0.98, 1.01)	0.99 (0.96, 1.02)	1.00 (0.97, 1.02)	1.00 (0.98, 1.02)	1.02 (1.00, 1.03)	1.02 (1.00, 1.04)	1.01 (1.00, 1.03)	1.02 (0.99, 1.04)
Diarrhea	1.02 (1.00, 1.03)	0.99 (0.97, 1.01)	0.99 (0.98, 1.01)	0.98 (0.96, 0,00)	0.99 (0.97, 1.01)	0.93 (-0.92, 0.95)[b]	0.99 (0.97, 1.00)[b]	1.00 (0.98, 1.01)	0.98 (0.97, 1.00)[b]	0.98 (0.96, 1.00)[b]

Abbreviations: OR, Odds ratio.

[a] Models are adjusted for maternal age, maternal education, maternal smoking, maternal stress, number of children in the household, calendar year of birth, birth month and grade. Analyses considering are furthermore adjusted for the effect of infections, and the analyses on infections are adjusted for the effect of fever.

[b] P-value< 0.05