Paper

Lupus
0(0) 1–10

DOI: 10.1177/0961203320973076
journals.sagepub.com/home/lup
SAGE

Systemic lupus erythematosus during pregnancy is not associated with school performance in offspring – A Danish population-based study

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Abstract

Introduction: Systemic lupus erythematosus (SLE) in pregnancy is considered a risk factor for a range of adverse outcomes in the offspring. Studies have indicated increased risk of neurodevelopmental disorders such as autism spectrum disorders, dyslexia and ADHD. However, the overall long-term cognitive development of children born to women with SLE has scarcely been examined. In this study, we compare test scores from the Danish National School Tests of children born to women SLE with children of the background population.

Methods: We included all singleton children born in Denmark between 1995 and 2008, who were listed in the Danish National School Test Register (n=738,862). Children born to women with SLE were identified through linkage of national healthcare registers. We assessed the children's performance in the national school tests between 2nd and 8th grade, in reading and mathematics. Information on the mothers' redeemed prescriptions in pregnancy was included in stratified analyses. Differences of mean test scores were derived from linear regressions and compared according to maternal SLE status, and predefined categories of medication exposures.

Results: In total, 312 (0.04%) children were born to mothers with SLE. There were no differences in performance in neither reading nor mathematics tests between those born to mothers with SLE and children born to mothers without SLE. When stratifying on medication exposures among children whose mothers had SLE, there was a non-significant tendency towards poorer results among those exposed to hydroxychloroquine and/or immunosuppressants (n=31), compared to those not exposed to these medications. A similar tendency was *not* observed among children whose mothers received hydroxychloroquine for non-SLE reasons (n=1,235)

Conclusion: This study indicates no major harmful effect on the child's neurocognitive development from exposure *in utero* to SLE, hydroxychloroquine and/or immunosuppressants, as measured by school performance.

Keywords

Pregnancy, systemic lupus erythematosus, child development

Date received: 6 July 2020; accepted: 22 October 2020

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Introduction

Systemic Lupus erythematosus (SLE) is a systemic autoimmune disease characterized by an inappropriate immune response, leading to high levels of autoantibodies and generalized inflammation. SLE primarily affects young women, and the course of the disease can be fatal if untreated.[1,2] Pregnancy poses a challenge for SLE patients, as active disease increases the risk for a number of adverse pregnancy outcomes for both mother and child.[3] Several medications, including hydroxychloroquine (HCQ) and glucocorticoids are effective in SLE. HCQ is recommended during pregnancies in recent years as it improves chances of favourable pregnancy outcomes among women with SLE.[4–6]

Unfortunately, little is known about long-term effects of the disease and its treatment on the children exposed *in utero*. This causes uncertainty and concern among both SLE patients and their healthcare providers, regarding the optimal strategy for care during pregnancy. As the disease is rare, observational studies require large cohorts, making them unfeasible in most settings, thus, population-based studies are an invaluable tool for addressing these questions.

The aim of this study was to assess long-term development of children born to mothers with SLE, measured by their school performance, including an investigation of the influence of medications frequently used in SLE pregnancies.

Materials and methods

Study population and setting

All live-born, singleton children born in Denmark between 1995 and 2008 (n=887,811) were identified from the Danish Civil Registration System.[7] Children who were deceased or had emigrated from Denmark before their 8th birthday, i.e., before the first school test, were excluded (n=19,871), as well as the 129,087 children not listed in the Danish National School Test Register (DNST) (i.e., most children attending private schools). In total, 738,862 children were followed until December 31st, 2017, death or emigration, whichever came first.

Exposure assessment

Maternal SLE exposure. The Danish National Patient Register (DNPR)[8] contains information on all in-patient visits since 1977 and out-patient visits since 1995, to Danish public hospitals. Diagnoses from each hospital visit were recorded according to the International Classifications of Disease (ICD) 10th edition from 1995 and the ICD 8th edition before that.[9,10]

Children were categorized according to maternal SLE status at time of birth; i.e. the mother had to be diagnosed with SLE before the child's date of birth for the child to be considered exposed. Maternal SLE was defined as the mother having at least two separate visits or hospitalizations with SLE as the main or secondary diagnosis (using ICD-8 code 7341 or ICD-10 code M32). All children not prenatally exposed to maternal SLE were included as reference population.

Medication exposures. To assess for possible effects of medications, we included information on the mothers' filled prescriptions during pregnancy. We chose to include medications frequently used in SLE pregnancies during the inclusion period, based on *a priori* clinical knowledge. Only medications with a high expected number of exposed children were included; thus, biological medications, etc., were not included, as they were not used routinely in SLE pregnancies before 2008. We defined categories of medications on basis of Anatomical Therapeutic Chemical classification (ATC) codes: "hydroxychloroquine/chloroquine (HQC)", "glucocorticoids", "any anticoagulants", "immunosuppressants", "Nonsteroidal anti-inflammatory drugs (NSAIDs)" and "paracetamol" (list of Anatomical Therapeutic Chemical classification (ATC) codes is provided in Supplementary Table 1). We considered the child exposed if the mother had filled at least one prescription from one month before the estimated date of conception to two weeks before the child's day of birth. We also examined the prescriptions filled within one year prior to conception and within one year after birth. We were not able to include information specifically on discontinuation of HCQ (or other medications) during pregnancy, which is a known risk factor for flares and, potentially, adverse pregnancy outcomes.[11] The Danish National Prescriptions Registry contains information on all filled prescriptions at any pharmacy in Denmark since 1995.[12] Over-the-counter purchases (e.g. of NSAIDs and paracetamol) and medication administered at hospitals are not included. Estimated date of conception was calculated by subtracting gestational age at birth, as registered in the DNPR, from the date of birth plus two weeks.

Danish National School Tests

The Danish National School Tests are mandatory tests, carried out in the Danish public schools since 2010. Approximately 85% of Danish children attend public schools, and some private schools participate voluntarily in the tests. The tests are computer-based, standardized adaptive tests, i.e., the difficulty of questions adapts to the skill-level of the child during the test, based on right and wrong answers.[13]

All children are tested four times in reading (Danish); in grades 2, 4, 6 and 8, and twice in mathematics; in grades 3 and 6. The test score is a measure of the child's skill level in the subject, and reported on a logit scale (−7; 7).

As the test scores for all tests followed normal distributions, the scores were standardized into z-scores, a measure of the relative position within the normal distribution of test-results. By definition, z-scores have a mean value of 0, standard deviation (SD) of 1 and the units are "standard deviations" (i.e., a pupil who has a z-score of 0 is on the 50th percentile and a pupil with a z-score of 1 is on the 84th percentile). Standardization into z-scores was achieved for each test score by subtracting the mean and dividing by the standard deviation for each specific test (subject/grade level/calendar year). Standardization makes it possible and appropriate to combine test results from multiple calendar years in the same analysis.[14]

Test scores from all reading and mathematics tests, from 2010 through 2017, were included in the study. The test results were provided by the Danish Agency for Information Technology and Learning (https://www.stil.dk/).

Covariates and other data

From Statistics Denmark,[15] we collected information on maternal educational level, parental nationality (country of origin), household socioeconomic status and parental cohabitation status. From the Danish Civil Registration System,[7] we had information on children's birth year, vital status, and maternal age at birth, and from the Medical Birth Register,[16] we had information on maternal smoking during pregnancy, birth weight and gestational age at birth. Continuous covariates were categorized as follows; maternal educational level: <=9 years; 10–14 years; >14 years of school; birth year of child: 1995–1999, 2000–2003, 2004–2008; maternal age at birth:<25; 25-35; >35 years; maternal smoking during pregnancy: yes/no.

Statistical analyses

Data were complete for exposure and outcome variables, but some covariate data were incomplete, mainly "maternal smoking in pregnancy" and "maternal education" (Table 1). To address this limitation, missing data was handled by multiple imputations, using the R package "mice",[17] using a chained equations approach, generating 15 complete datasets.

Maternal SLE and school test performance. For the main analyses we assessed the difference in school test performance of maternal SLE exposed children compared to unexposed children. Using multiple linear regression models, we calculated the difference of mean z-score between the exposed and unexposed, with 95% confidence intervals, adjusting for maternal age, maternal educational level, maternal country of origin, and smoking in pregnancy. This was done separately for each test (i.e., by grade level and subject). Potentially confounding covariates were chosen from *a priori* knowledge of the subject matter, incorporated into a directed acyclic graph of the study hypothesis.[18] We did not adjust for potential mediating factors, such as birth variables, because these factors might be on the causal pathway and can introduce collider stratification bias.[19] We used cluster robust standard errors,

Table 1. Descriptive characteristics of 738,862 singleton children born in Denmark 1995–2008 who were listed in the register for Danish National Tests, according to maternal Systemic Lupus Erythematosus (SLE) at birth.

Child/parental characteristics	No maternal SLE (n = 738,550), n (%)	Maternal SLE (n = 312), n (%)
Sex		
Male	379,510 (51)	158 (51)
Female	359,040 (49)	154 (49)
Birth year		
1995–1999	264,503 (36)	81 (26)
2000–2003	218,766 (30)	86 (28)
2004–2008	255,281 (35)	145 (46)
Maternal age		
Mean age, years (±SD)	30.01 ± 4.78	31.23 ± 4.40
Smoking in pregnancy		
Nonsmoker	448,096 (61)	191 (61)
Smoker	99,091 (13)	45 (14)
Missing	191,363 (26)	76 (24)
Child order		
First born	318,510 (43)	149 (48)
Second child or more	420,040 (57)	163 (52)
Maternal education		
<= 9 years	153,876 (21)	67 (21)
10–14 years	358,707 (49)	160 (51)
>=15 years	208,400 (28)	73 (23)
Maternal nationality		
Missing	17,567 (2)	12 (4)
Danish	652,176 (88)	274 (88)
Other nationality	86,374 (12)	38 (12)
Maternal civil status		
Single	87,667 (12)	50 (16)
School tests		
Never tested	10,458 (1)	9 (3)
Birth variables		
BW, mean grams (±SD)	3,535.7 ± 563.5	3,101.6 ± 675.9
BW <2500g	24,772 (3)	50 (16)
GA, mean days (±SD)	278.5 ± 12.58	269.9 ± 16.
GA <37 weeks	36,047 (5)	59 (19)

BW: birth weight; GA: gestational age.

clustering on mothers, to account for dependence between siblings' test scores (using the cluster function from the "miceadds" package in R).[20]

Maternal SLE, medications and school test performance. To assess the impact of exposure to medication, we divided SLE exposed children according to the medication exposures *in utero*; children exposed to SLE *and* medication were compared to all children not exposed to SLE, for each defined category of medication. Because few children of mothers with SLE were exposed to the individual medications and in order to improve statistical power, we combined types of SLE medication exposures into three groups representing a proxy for SLE disease severity: 1) HCQ and/or immunosuppressants, 2) other included types of medication 3) no included type of medication. The group "HCQ and/or immunosuppressants" is considered to represent the highest maternal SLE disease severity since, during the inclusion period, it was not yet common to extend these treatments into pregnancies, unless there was active disease not controllable with glucocorticoids. The exposure groups are disjunct and hierarchical, and each child was only included in the highest level of exposure for which they fulfilled the criteria. We calculated mean z-score differences, with 95% confidence intervals for each of these three combined exposure groups using all children not exposed to SLE as reference. The analyses were adjusted for maternal age, maternal educational level, maternal country of origin, and smoking in pregnancy and we used cluster robust standard errors, clustering on mothers.

To evaluate if HCQ exposure in itself was associated with test z-scores, we performed the following (post hoc) sensitivity analyses: Including only the children exposed to maternal SLE, we compared test scores of the children exposed to HCQ *in utero*, with the children whose mothers only redeemed HCQ within one year prior to conception AND within 1 year after birth of the child (i.e., not during pregnancy); the remaining SLE exposed children served as the reference group. Finally, including only children *not exposed* to maternal SLE, we compared the test z-scores of children exposed to HCQ (for other indications than SLE), to children not exposed to HCQ.

A priori *planned sensitivity analyses*

Because the study population was restricted to children having a measure of the outcome, i.e., any school test results, we sought to address the potential selection bias inherent to this design by performing an inverse probability (for selection) weighted analysis. The method is further described in Supplementary 4. We also calculated adjusted odds ratios for being exempt from testing due to "mental or physical impairment" (as recorded by teachers in the DNST), to assess if risk of exemption was associated with exposure status, thus potentially leading to selection bias (adjusting for birth year, maternal age, maternal nationality, and smoking in pregnancy).

The individual school tests can be viewed as a time series of repeated, correlated measurements (though with an only partially overlapping population of children in each test). To evaluate the importance of random effects at the child (and mother) level causing this correlation, we fitted multilevel mixed effects regression models. We combined z-scores from all grades and calendar years, as repeated measurements nested within children and children within mothers (thus allowing for random effects at the child and mother levels) and ran the model separately for reading and mathematics.

We performed stratified analyses on sex to examine differences between SLE exposed boys and girls.

All data were collected and hosted at servers by Statistics Denmark; a government owned agency. Owing to the privacy protecting rules of Statistics Denmark, any results based on fewer than five individuals cannot be reported. The study was approved by the Danish Data protection Agency under the Aarhus University common agreement (j. number 2015-57-0002) and Aarhus University j. number 2016-051-000001, sequential number 737. According to Danish legislation, ethical approval and informed consent was not required, as all data were anonymized prior to access.

All statistical analyses and graphs were made using R version 3.5.2.[21]

Results

The final study population consisted of 738,862 children, including 312 children born to mothers with SLE. Descriptive characteristics of exposed and unexposed children are shown in Table 1.

In general, mothers with SLE were slightly older (31.2 years vs 30.0 years), and the exposed children were more often first born, and born in the later years of the inclusion period. The numbers of children exposed to SLE medications are presented in Table 2; the numbers were generally low, for all included types of medication. Only 47% of mothers with SLE filled any prescription for SLE medication during pregnancy.

Of the 867,940 children eligible for participation, 15% were excluded from the study because they were not listed in the DNST (i.e. had no measurement of the outcome); this constituted 20% of all SLE exposed (n=77/389) compared to 15% among the unexposed (129,001/867,551). There were no major differences

Table 2. *In utero* medication exposures by school test, among 312 Danish children born to mothers with SLE, defined by prescriptions filled by the mother during pregnancy.

	Gluco-corticoids (N = 94)	NSAIDs (N = 29)	HCQ (N = 16)	Anti-coagulants (N = 65)	Immuno-suppressants (N = 17)	HCQ/ immunos. (N = 31)	Any SLE prescription (N = 147)
Reading 2nd grade	58	14	8	53	17	23	97
Reading 4th grade	51	15	≤5	35	9	12	76
Reading 6th grade	40	14	6	21	≤5	10	58
Reading 8th grade	34	12	6	12	0	6	48
Maths 3rd grade	52	16	≤5	41	11	14	83
Maths 6th grade	42	14	7	21	≤5	11	60

Abbreviations and ATC codes: Glucocorticoids (H02AB-); NSAIDs: Non steroidal anti inflammatory drugs (M01A-); HCQ: hydroxychloroquine (P01BA-); Anticoagulants (B01-, N02BA01); Immunosuppressants (L0-); HCQ / immunos: hydroxychloroquine and/or Immunosuppressants (P01BA-, L0-)

between the study population and the excluded populations (Supplementary Table 2).

Among the children recorded in the DNST, 20,384 children, including 11 SLE exposed children, were ever granted exemption from testing due to mental or physical impairment (adjusted odds ratio: 1.24 (95% CI: 0.6; 2.4) for children born to mothers with SLE compared to children of mothers without SLE)

Main analyses

There was no difference in school test performance, in neither reading nor mathematics test, between children exposed to maternal SLE and children not exposed to maternal SLE (Figure 1). Superimposed frequency-histograms of z-scores, by exposure to maternal SLE, are shown in Supplementary 3.

We compared children exposed to SLE *and* related medications to all children not exposed to SLE (regardless of any medications). Exposure to SLE *and* glucocorticoids, aspirin or other anticoagulants were not associated with any trend towards poorer test performance (data not shown). Maternal SLE and prescription NSAID use was associated with a slight trend towards poorer performance in the lower grade levels, though not significant (data not shown). No analyses were feasible for prescription paracetamol use due to low number of children of SLE mothers identified as exposed (n=7). HCQ (n = 16) and immunosuppressants (n = 17) were also rare exposures, making separate analyses for each of these drugs unfeasible.

Of the 312 children exposed to maternal SLE, 31 (10.0%) were exposed to HCQ and/or immunosuppressants. These children tended to perform worse in all tests compared to the children of mothers without SLE (Figure 2), although the uncertainty of the estimates is high due to low numbers. The children of mothers with SLE who only redeemed prescriptions for any of the other included types of medication, or none at all, during pregnancy had scores similar to the children of mothers without SLE (Figure 2).

When comparing test scores of the children exposed to SLE *and* HCQ, to children whose mothers discontinued HCQ around pregnancy (defined as the group who filled prescriptions in the year prior to conception and the year after birth, but not during pregnancy (n=18)), there was no clear difference between the two groups (data not shown, due to low numbers).

There was no tendency towards poorer test results among 1,235 children whose mothers did *not* have SLE, but who *had* filled a prescription for HCQ during pregnancy (likely for malaria-prophylaxis, Sjogren's disease or rheumatoid arthritis), as compared to children with neither exposure (Figure 3).

Sensitivity analyses

The inverse probability weighted analysis was in accordance with the main results (Supplementary 4).

Combining tests at all grade levels in one multilevel mixed effects analysis did not change results; there was no difference between the SLE exposed children and

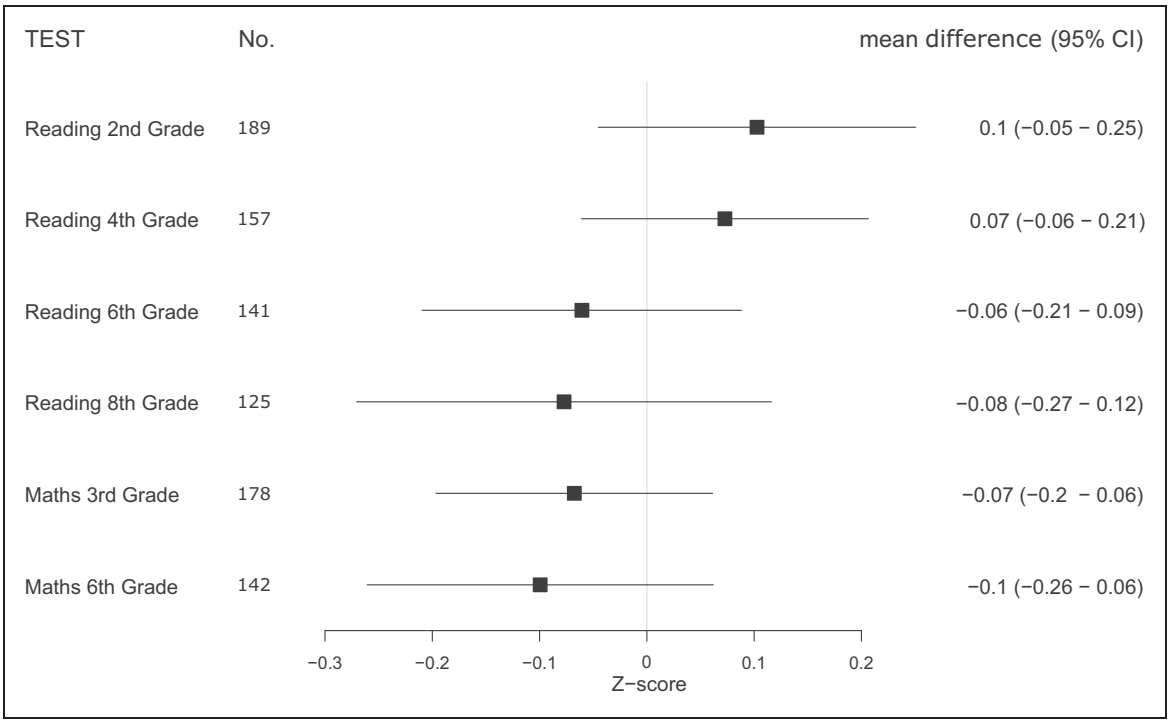

Figure 1. Adjusted* mean test score differences in Danish national school tests, by exposure to maternal SLE, among 738,862 Danish children. The box indicates adjusted mean score of SLE exposed children, the bar indicates 95% confidence interval; reference group was children not exposed to maternal SLE, marked by grey line. *Adjusted for maternal age, maternal educational level, maternal nationality and smoking in pregnancy.

the SLE unexposed children (mean score difference in reading of −0.02 SD (95% CI: −0.08; 0.05) and in mathematics of −0.12 SD (95% CI: −0.19; 0.05)).

Sex-stratified analysis did not point towards any difference between boys and girls (Supplementary 5).

Discussion

Overall, we found no difference in the test performance of children according to maternal SLE status. We found that the proportion participating in Danish national school tests were slightly lower among children whose mothers had SLE, however the inverse probability weighted analysis did not point towards bias of the results due to selection.

The number of prescriptions for SLE medications filled during pregnancy was lower than expected; e.g., only five percent of mothers with SLE filled a prescription for HCQ during pregnancy. However, when combining categories of medication, the use of medications indicative of high disease severity (immunosuppressants and/or HCQ) was associated with a tendency towards poorer test performance in the children, when compared to the SLE exposed children where the mother did not use these medications in pregnancy.

Strengths and limitations

In this large nationwide study, we were able to include all children born to mothers with an SLE diagnosis, during a period of more than 20 years. This resulted in the inclusion of more than 300 children born to mothers with SLE. Furthermore, we were able to utilize the results from national standardized school tests as an indicator for child development.

In Denmark, healthcare is universal and free for all residents. The DNPR includes all contacts to public hospitals and is virtually complete.[8] As SLE is a condition requiring specialized care, we expect all SLE patients to be diagnosed and treated in public hospitals, thus identifiable from the registers. This is supported by another Danish study, that did not identify any SLE patients from the primary healthcare system, who were not already registered in the DNPR.[22] The sensitivity of the SLE diagnosis in the DNPR is estimated to be high.[22,23] A recent study on incidence of SLE in Denmark found a positive predictive value of *one* SLE diagnosis in the DNPR of ∼70%, but this increased to >80% when additional contacts were included.[2] For this reason, we required >1 hospital contact with SLE, to ensure a high validity of the SLE exposure definition.

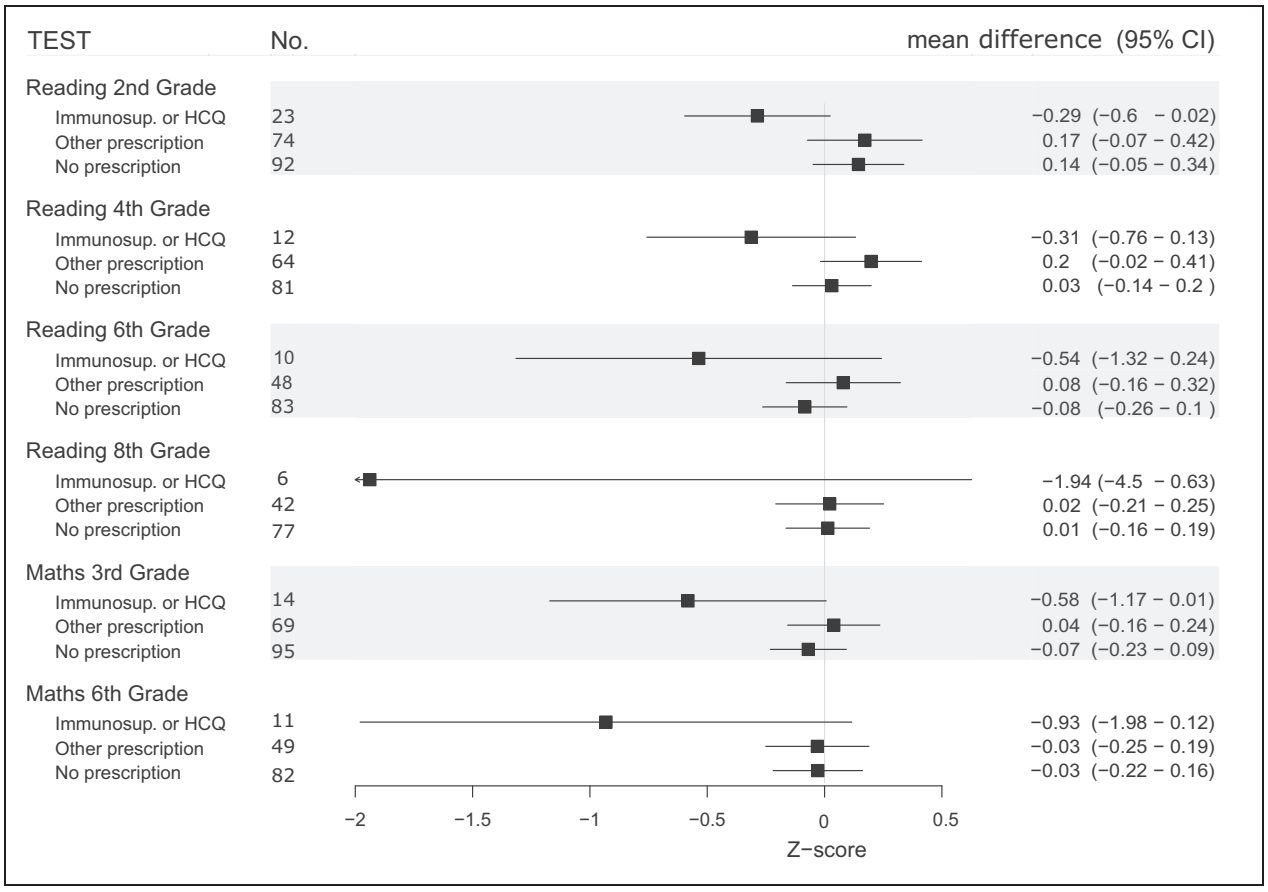

Figure 2. Adjusted* mean test score differences in Danish national school tests of children born to mothers with SLE who redeemed different categories of medication during pregnancy, compared to children of mothers without SLE, regardless of medication (grey vertical line), among 738,862 Danish children. *Adjusted for maternal age, maternal educational level, maternal nationality and smoking in pregnancy. Medication categories: defined as mothers' redeemed prescriptions in pregnancy: "Immunosup. or HCQ": any immunosuppressants and/or hydroxychloroquine; "Other prescriptions": any glucocorticoids, anticoagulants, NSAIDS or paracetamol; "No prescriptions": none of the above.

The Danish national school tests provide a marker of cognitive and psychosocial development of children through the age span of approximately 8 to 15 years. The school test results contain information on all children in the cohort on a continuous scale. This is an advantage compared to the dichotomous outcomes of diagnoses, such as neurodevelopmental disorders, which does not provide information on the majority of children without these diagnoses. The test scores have, as is true for any school test or exam, a degree of uncertainty at the individual level. Other factors than skill level can affect the test score, e.g., concentration or motivation. However, this is unlikely to affect children born to mothers with SLE differently than children born to mothers without SLE, and we consider the scores robust with regards to comparison of larger groups. As the population of children participating in each test overlapped, we considered the tests a form of repeated measurements with a degree of correlation, thus Bonferroni corrections were not applied. Unfortunately, we did not have data on final exam grades or higher education.

The information on prescription medication captured by the Danish Prescription Registry is essentially complete,[12] and based on automated electronic reports generated from the barcodes of prescription medicines when dispensed. Using prescription data to define exposure groups for medication is a commonly used tool;[24–26] however, the approach poses several challenges, especially in pregnancy studies. There is an uncertainty as to whether the medications have been used by the mothers, and for how long. We also cannot rule out that mothers who did not fill prescriptions, took medication they were in possession of prior to the pregnancy. Some women might have stopped taking their medications during the pregnancy, perhaps when they discovered they were pregnant. Owing to this, exposure levels might vary

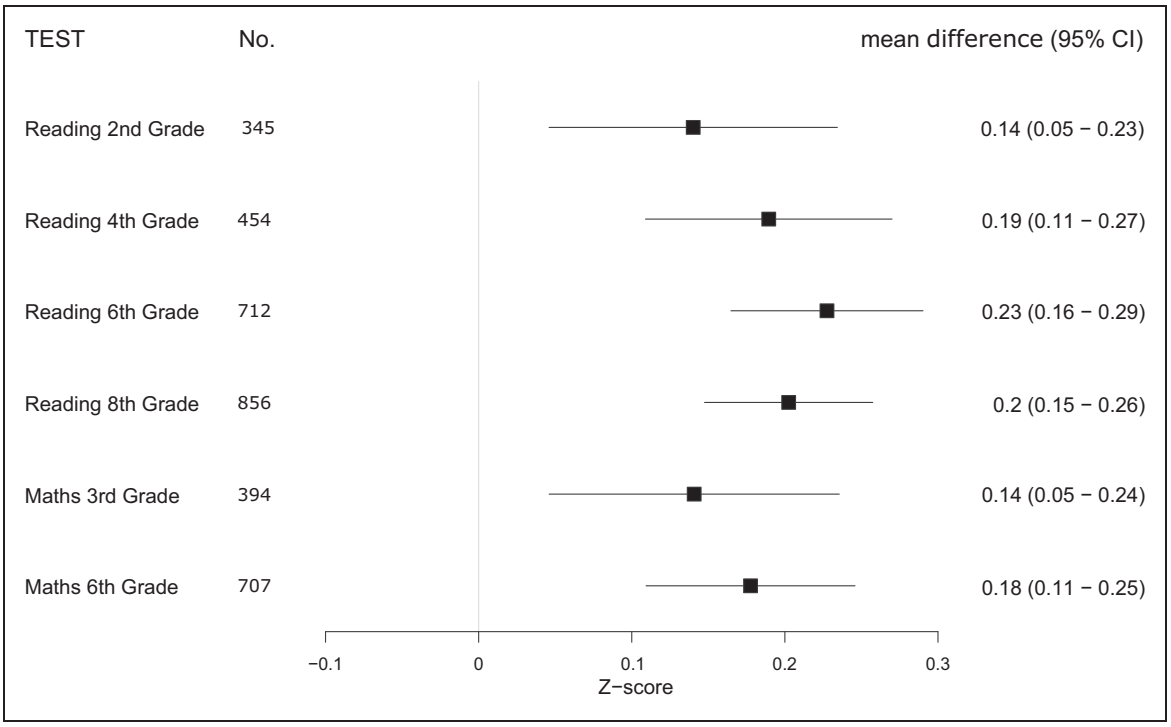

Figure 3. Adjusted* mean test score differences in Danish national school tests from children where the mother redeemed HCQ in pregnancy compared to children where the mother did not redeem HCQ in pregnancy (grey line) among 738,550 Danish children born to mothers ***without*** SLE. *Adjusted for maternal age, maternal educational level, maternal nationality and smoking in pregnancy.

considerably with regards to timing, duration, and dosage. Other studies found that SLE patients generally take less HCQ than prescribed, both when not pregnant[27] and when pregnant.[28,29] Clinical recommendations have changed since the time of inclusion for this study and HCQ is now recommended in all SLE pregnancies.[30]

The study's design introduces a risk of selection bias, as children without any school tests may differ from children with school tests. Some children without test results might have a physical or mental impairment, causing them not to be tested, or to even attend a public school, thus they would be excluded from this study. As shown in Supplementary 2, the percentages of children with congenital malformations or syndromes and psychiatric diagnoses were only slightly higher among children of mothers with SLE, and comparable among the children who were listed and not listed in the DNST. Moreover, the inverse probability (for selection) weighted analysis did not indicate any major selection bias.

As in other observational studies there is a risk of confounding. Only few covariates ended up being considered true potential confounders and thus included in the models. This was due to the timing of the main exposure: the intrauterine exposure to maternal disease takes place before any exposures during birth or in the upbringing, thus these subsequent exposures cannot be true confounders. We were able to adjust for the factors considered to be the strongest potential confounders and that have been shown to be strong predictors of school test results; e.g., parental education and nationality. Children of SLE mothers performed similarly to their peers in school tests, even though they were more often born premature or with low birth weight.

Interpretation

In a systematic review from 2017, Yousef Yengej et al. reviewed the physical, neurocognitive and psychiatric development of offspring from mothers with SLE.[31] They included 28 studies and found several reports of greater risks of learning disorders, dyslexia and autism spectrum disease, especially among male offspring. Most included studies were small, with low power, and results were contradicting. In our study, we found no overall difference on test performance, and though learning disorders might lead to children being exempt from testing in severe cases, we did not see that children of mothers with SLE had a markedly higher risk of exemption. Our sex-stratified analysis did not point towards male offspring being differentially

affected, they even tended to perform better than their peers in reading test, when adjusting for confounding factors.

The Danish national school test results have been shown to predict final exam results which are correlated with future education and career.[13,32] In other settings, standardized test scores were found to be predicted by IQ levels,[33] but this has not been assessed for the Danish school tests. As such, it might not be appropriate to make direct comparisons between school test performance and studies reporting on other neurocognitive or neurodevelopmental outcomes, however, no other studies on school test performance including reading or mathematics skills, were found.

Few children in the study were identified as exposed to medications typically used to treat SLE. The children in our cohort were all born prior to 2009, and the use of medication in pregnancies has since changed for SLE patients in Denmark, along with treatment recommendations. In a Danish study from 2015 on HCQ and SLE, authors found that approximately 30% of newly diagnosed SLE patients would redeem HCQ within the first year after diagnosis, with an increasing trend in recent years.[34] In a nationwide Swedish study including SLE pregnancies from 2006-2012, Palmsten et al. found that disease modifying anti-rheumatic drugs (DMARDs) including HCQ had been redeemed in 49.3% of SLE pregnancies. Several studies have focused specifically on the use of HCQ in pregnancy; mainly assessing the association with birth outcomes. Balevic et al. studied medication use in pregnant SLE patients and found that the highest measured levels of HCQ (indicative of good adherence to medication) coincided with the highest maternal disease activity, and was not associated with more favourable birth outcome; however only 27 SLE patients were included.[29] Contrary to this, another study found that discontinuation of HCQ in pregnancy was associated with higher disease activity, and the women who continued HCQ had lower disease activity and more favourable birth outcomes.[5] In our study, we considered the use of HCQ and/or immunosuppressants as indicative of more severe disease, because at the time of inclusion these medications were not yet recommended during pregnancies. Exposure to HCQ without exposure to SLE was not associated with poorer test performance, thus, we do not suggest that HCQ in itself is affecting foetal cognitive development. There are, however, many potential pitfalls when comparing groups exposed to HCQ for different indications; e.g. the dosage, duration and timing of exposure might be different. These issues will have to be addressed in additional studies.

In Conclusion, this study did not identify a negative association between exposure to maternal SLE *in utero* and long-term child development as measured by academic performance. The number of pregnant women with SLE who used SLE medication was low and specific effects of medication and disease activity must be studied further.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr. Christensen reports personal fees from Eisai and UCB, during the conduct of the study. All other authors declare that there are no conflicts of interest.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by The Danish Rheumatism Association and Aarhus University. Furthermore, Jacob Christensen was supported by the Central Denmark Region, the Danish Epilepsy Association, and the Novo Nordisk Foundation (NNF16OC0019126). Bent Deleuran was supported by The Danish Rheumatism Association and AUFF NOVA (2016-9-27).

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