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Prenatal exposure to nicotine and impaired reading performance

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Abstract

Objective—To investigate whether prenatal exposure to nicotine has an impact on several reading skill outcomes in school age children.

Study design—Using a longitudinal sample of 5,119 school age children in the Avon Longitudinal Study of Parents and Children (ALSPAC), this study investigated specific reading skill outcomes in the area of speed, fluency, accuracy, spelling and comprehension in relation to prenatal nicotine exposure, after adjusting for potential mediators and confounders. Prenatal nicotine exposure was divided into three categories: high (>17mg per day), low (≤17mg per day) and no exposure.

Results—We found that prenatal nicotine exposure was associated with increased risk of underperformance in specific reading skill outcomes after adjusting for potential mediators and confounders ($p = .006$). The effect of poor performance in decoding single words was most pronounced among children with prenatal exposure to high levels of nicotine in conjunction with a phonological deficit. Overall the results showed that maternal smoking has moderate to large associations with delayed or decreased reading skills of children in the ALSPAC.

Conclusions—High prenatal nicotine exposure has a negative association with reading performance in school age children. In addition, modeling showed that environmental factors significantly moderated the interaction between prenatal nicotine exposure and reading skill outcomes.

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Keywords

Reading performance; reading skills; prenatal exposure to nicotine; ALSPAC

Reading is a critical skill that has profound social, health and economic implications for life-course development. A significant proportion of the population will have unexpected reading difficulty. Such difficulty (often set at 1.5 SD below developmental expectations) among children and adults who otherwise have the intelligence and instructional opportunities necessary for accurate and fluent reading is the primary identifier of reading disability (RD). Worldwide, the prevalence of RD ranges from 7 to 17% among school age children[1–3]. Understanding factors that account for variability in reading performance is therefore critical to understanding and preventing RD. Cigarette smoking exposes the developing fetus to nicotine and may be an unexplored but significant environmental risk factor for variability in reading skill. Despite multiple studies that have validated the adverse consequences of smoking during pregnancy[4], approximately 9% of pregnant women smoke although estimates as high as 37% have been reported[5, 6].

Numerous studies have investigated the relationship between maternal smoking during pregnancy and various cognitive and behavioral indices[7]. Maternal smoking has been associated with reduced performance on tests of intelligence, academic achievement, short-term and verbal working memory, long-term and immediate memory for auditory/verbal material, executive function, increased incidence of behavioral disorders during childhood and adolescence, hyperactivity, and attention deficit. Animal studies support biological evidence for accelerated motor activity, neurobehavioral, learning and memory deficits, and alteration of neurotransmitter function due to exposure to nicotine *in utero*[8]. In addition, a large human study[9] found decrements in reading ability attributed to maternal smoking. Observational studies in humans have shown mixed results due to bias from unmeasured and confounding factors, and small, unrepresentative sample sizes.

To address the shortcomings in previous studies and to test the hypothesis that prenatal nicotine exposure has specific effects on reading, we investigated the association of prenatal nicotine exposure and specific reading skills measured at age 7 or 9 years among children in the Avon Longitudinal Study of Parents and Children (ALSPAC). The overall goal was to cover multiple dimensions of the reading construct (e.g., decoding, single-word identification, fluency and comprehension) with a rich set of social and environmental variables in modeling the association between maternal smoking and reading skills.

Methods

The ALSPAC is a large population cohort of 15,211 children born in 1991 and 1992 in Bristol, England. The core ALSPAC sample consists of 14,663 children[10]. Among children who had any reading assessments at age 7 and 9 (n=6,823), we excluded those with Wechsler Intelligence Scale for Children (WISC-III) total IQ score[11] equal to or below 75 (n=876) to minimize potential confounding effects from comorbid cognitive syndromes. Altough the diagnosis of Intellectual Disability (ID) requires an assessment of IQ below approximately 70, the standard error of most relevant measures is 5. The cutoff for this study was chosen to ensure that individuals with IQ who may or may not meet the other criteria of ID (e.g., adaptive functioning) were not over-excluded. We also excluded children who were born outside of the two main maternity wards (n=717) because they had limited perinatal information, and twins (n=111). Our final sample contained 5,119 children. Ethical approval for the study was obtained from the ALSPAC Law and Ethics Committee, the Local UK Research Ethics Committees, and the Yale Human Investigation Committee.

Information on maternal cigarette smoking was obtained from self-reported postal questionnaires completed by mothers between gestational age 8–42 weeks, and 8 weeks post delivery. Daily intake of nicotine was calculated by multiplying the number of cigarettes per day by the nicotine content of each brand of cigarettes smoked. On the basis of previous studies[12, 13] and because there was not enough statistical power to divide smokers into three trimester time periods, we derived the prenatal exposure to nicotine variable by taking the maximum amount of nicotine from the four time points. Smoking was then classified into three groups: no exposure, low exposure (≤17 mg of nicotine per day) and high exposure (>17 mg of nicotine per day)[14]. The cutoff of 17mg nicotine per day is the approximate minimum of one pack (20 cigarettes) of average strength cigarettes[14].

We investigated the following seven specific reading outcomes: reading speed, single-word identification, spelling, accuracy, real and nonword reading, and reading comprehension. The reading speed, accuracy and comprehension scores were standardized measures at age 9 from the revised Neale Analysis of Reading Ability (NARA II)[15]. The child read passages from a booklet or stories then was asked a series of questions about the content of the story. The reading speed score was a standardized measure of the number of words read per minute, with comprehension questions asked as soon as the child had finished reading. Single-word identification was assessed at age 7 with the reading subtest of the Wechsler Objective Reading Dimensions (WORD)[16]. Pictures and words were used to assess decoding and word reading. The final reading score was obtained by computing the sum of the number of items the child read or responded to correctly. WORD spelling was assessed at ages 7 and 9 with a series of 15 age-adjusted words. The final spelling score was the average of scores at age 7 and 9. The real words and nonword reading scores were assessed by asking the child to read ten real and ten nonwords out loud at age 9[17]. Both the words and non-words were specifically chosen from a larger selection of words taken from research conducted by Terezinha Nunes and others in Oxford[17]. As a secondary analysis, we also used the comprehension component of the Reynell Developmental Language Scale[18] at age 25 months to explore early language development factors. This measure focuses on the understanding or comprehension of spoken language.

We assessed the impact of several comorbid conditions previously associated with maternal smoking and maternal alcohol consumption during pregnancy[19], and ADHD[20]. ADHD was assessed through the Development and Well-Being Assessment (DAWBA)[21] DSM-IV clinical diagnosis at 91 months. We also examined birth weight and gestational age because these have been associated with prenatal smoking. We adjusted for neonatal resuscitation due to the reported association of hypoxic/ischemic brain injury and cognition[22]. In addition, we included the following covariates in the multivariable model: mother's age at delivery, social class, alcohol consumption during pregnancy, marital status, general verbal interaction, specific interactions around literacy[23], antenatal class attendance, child's sex, ethnicity, and type of school. The literacy and verbal based interaction terms were derived from information on frequency of mother or other caregivers reading (literacy) to the child during age 5–8 years and talking (verbal) to the child when doing another task during age 3–5 years.

Furthermore, we designed our analysis to include the effect of phonology because of strong evidence that identifies this skill as the core cognitive and linguistic ability that drives early acquisition of reading skills[24]. Children with RD underutilize temporoparietal (TP) structures, and those resistant to intensive phonologically-based interventions fail to show increased TP processing or connectivity with other involved regions[25]. As a result, our model prioritized phonology using the phoneme awareness score based on performance on the phoneme deletion task of the WORD. In addition, we considered this factor as a

potential effect modifier of the relationship between prenatal exposure to nicotine and each individual reading skill outcome.

To assess and characterize covariates for potential confounding or mediating effects, we evaluated the total set of 15 covariates in two subsets. Subset one consisted of covariates that were independent of the timing of the nicotine exposure: mother's age, social class, marital status, literacy and verbal interaction with the child, status of antenatal class attendance, child's sex, ethnicity, and type of school. Subset two consisted of covariates that were concurrent with or occurred after the time of prenatal exposure and may have been affected by the downstream biological impact of the exposure: ADHD, neonatal resuscitation, birth weight, alcohol consumption, phonology, and gestational age.

Missing data description and methods

The seven specific reading outcomes were assessed at either the age of 7 or 9 study data collection points. Thus, children who did not participate in either of these clinic visits were excluded. To characterize the degree of bias that this created, we compared those who were included against those excluded on general demographics and other factors. Table I (available at www.jpeds.com) shows distributions of covariates and comorbidities between the analysis sample (Sample A) and the remainder of the cohort (Sample B). Although there were demographic differences between the analyzed and the overall sample, none systematically biased the analysis sample toward lower reading scores.

The variables in the ALSPAC dataset were collected at different times from an array of sources including schools, parents, self-reports and hospital records. As a result of missing values, the total sample analyzed in each model varied slightly. To validate our results, we compared our results with complete data containing multiple imputed values using MI and MIANALYZE in SAS 9.1.3. We compared the results from models using the multiple imputed datasets with models using all individuals who had assessments at age 7 and 9 in the ALSPAC (n=5,119). The imputed data models generated increased precision for estimates of model parameters due to smaller standard errors, but the substantive results were equivalent to the complete data analysis.

Statistical analyses

We first performed multivariate analysis of variance (MANOVA) to test for a global effect of nicotine on all reading outcomes. We then fit crude and multivariable regression models with prenatal exposure to nicotine as the predictor for each continuous reading outcome. To explore mediation effects, we sequentially added covariates from set two to the model with all set one covariates. We used SAS 9.1.3 in all our analyses and procedures.

RESULTS

Sample characteristics of those individuals included in our study and the distribution of confounders across the three nicotine exposure groups are shown in Table II. Overall, males and females were distributed almost equally. The majority of subjects were White. Among the mothers, 85.9% were classified in a non-manual labor social class, and 67.4% attended antenatal class. Most children (95.3%) were born at full term (≥37 weeks of gestational age). Higher proportions of mothers were classified in a manual labor social class for low (23.9%) and high (37.5%) exposure groups compared with the no exposure group (11.9%). Mothers were more likely to be married for no (87%) or low exposure (70.1%), compared with high exposure (61.3%).

The seven reading outcomes had pairwise correlations ranging from 0.54 to 0.84 (Table II; available at www.jpeds.com). The WORD reading or single-word identification and spelling

skills outcomes had the highest correlation. Outcomes were compared across the three nicotine exposure categories in Table IV (available at www.jpeds.com). The high nicotine exposure group exhibited the lowest mean values across all the reading outcomes.

Prenatal exposure to nicotine was a strong global predictor across the seven reading outcomes taken together in the adjusted model (Wilks' lambda = 0.989; $p = .006$). Next we performed regression analyses for each individual reading outcome (Table V). The crude analysis, where we analyzed the relationship between each reading outcome and prenatal nicotine exposure alone, showed strong evidence of association for each individual reading outcome ($p < .0001$). The nonword reading outcome showed some evidence for association although it was not as strong ($p = .02$). For all reading outcomes there was a strong negative correlation with prenatal exposure to nicotine, with most of the effect attributable to the difference between high exposure and no exposure groups.

In our final multivariable model (Table V) composed of all 15 covariates, prenatal nicotine exposure remained a strong predictor for all outcomes (except for nonword reading): reading speed ($p = .03$), single-word identification ($p = .01$), spelling ($p = .0002$), accuracy ($p < .0001$), real words reading ($p = .0001$) and reading comprehension ($p < .0001$). Overall the beta coefficients indicated a reduction in reading skills associated with each subsequent level of nicotine exposure. After adjusting for covariates, the significant associations observed for the low nicotine exposure group in the crude analyses remained significant for accuracy and comprehension. Among the covariates included in the final adjusted models, phonology, attendance in antenatal class, literacy based interaction with the child, and maternal social class consistently showed strong associations in all seven outcomes.

For each reading outcome, we assessed the effect of interaction between phonology and prenatal exposure to nicotine. Although the global interaction between phonology and prenatal exposure to nicotine was borderline significant for real words reading ($p = .05$), the specific interaction between phonology and high nicotine exposure during pregnancy predicted real words reading ($p = .02$). To investigate this relationship further, we examined the distribution of mean values for reading outcomes across the three exposure groups and dichotomized phonology at the median value (Table VI). These results show that the combination of low phonology scores and high levels of nicotine exposure were associated with the lowest reading scores. To test for a contribution from early language development we performed additional secondary analyses by looking at Reynell Developmental Language Scale scores for a small subset of the study cohort (n=456). The multivariate model results did not show any significant relationships with respect to the main predictor.

Assessment of covariates and comorbidities

To ensure that our IQ exclusion criteria did not bias our estimate of the nicotine-reading relationship, we unrestricted IQ and performed a sensitivity analysis that included it as a covariate. We found a slightly attenuated but persistently significant association between nicotine exposure and the reading outcomes (data not shown), supporting exclusion based on IQ, and consistent with the recent literature[26].

We attempted to distinguish potential mediators and confounders through a two-step modeling approach. The main association between reading outcomes and nicotine exposure persisted between both models. Of interest, the literacy-based interaction term was a significant positive predictor ($p < .0001$) for all reading outcomes, but dropped to nonsignificance when downstream predictors were added to the model for three of the reading outcomes. A follow-up analysis that sequentially added set two covariates individually to set one, indicated that phonology, acting as a strong negative mediator, was the factor that diminished the mother-child interaction effect in the second model.

DISCUSSION

To date, specific reading skills have not been thoroughly investigated in relation to maternal smoking during pregnancy. In the current study, we investigated the impact of prenatal exposure to nicotine on specific reading skill outcomes among children in the ALSPAC and found a global association with reading. After identifying, assessing and adjusting for a wide range of covariates, high prenatal exposure to nicotine demonstrated persistent and robust associations across six (of seven tested) specific reading outcomes. The results show that maternal smoking has moderate to large associations with delayed or decreased reading skills.

The nonword reading outcome was not associated with prenatal exposure to nicotine in the final model. This may be because nonword reading only requires skills to decode letters and to translate them to sounds without linking the word to a meaning. The slightly lower, but still moderate association with other reading skills ($r = .54 – .70$ versus the overall range of associations among reading skills of $r = .64 – .84$) is consistent with studies showing that nonword reading is supported by distinct neurobiological systems[26,27].

We observed and examined substantial moderating effects of phonology on the relationship between smoking and single word reading. Our analyses showed that the combination of low phonology scores and high levels of prenatal nicotine exposure were associated with especially depressed single-word reading scores (Table VI). Children with the weakest reading skills may have had impaired phonological processing for other reasons (e.g., genetic) and prenatal exposure to high levels of nicotine accentuated its effect on reading, perhaps as a cognitive risk factor by environment interaction. Alternatively, prenatal exposure to high levels of nicotine may depress non-phonological functions, such as recall and memorization skills. For this reason, the group with prenatal exposure to high levels of nicotine compared with the low and no exposure groups may rely on phonological ability to compensate for deficiency in recall or memorization skills, especially for single-word reading tasks. The fact that phonology attenuated the strong effect of mother-child interaction time suggests that mother-child interaction time has a strong positive effect on reading ability, but this effect can be overwhelmed by phonological deficits. These results bolster the idea of early appropriate and targeted intervention to assist in phonological development.

A variety of factors including prior language and reading abilities influence reading outcomes. Although reading is a dynamic developmental skill, with multiple influences that change over the course of early to middle childhood[28], our results show that associations with smoking are robust across multiple reading dimensions even after adjusting for many of these influences.

The ability to specifically target nicotine dosage in our current study is pertinent to the mechanism of nicotinic acetylcholine receptors (nAChRs), which are key mediators in brain development and are present very early in the fetal brain. Potential mechanisms of direct effects of nicotine result from the interactions of nicotine with nAChRs to produce changes in ion fluxes. Studies have shown maternal smoking is associated with global increases in DNA methylation[29]. A recent study showed that maternal smoking increased epigenetic modifications of the brain-derived neurotrophic factor (BDNF) gene[30], potentially having critical consequences on the structure of the brain. However, studies have not yet directly linked maternal smoking affects to behavioral outcomes through an epigenetic mechanism.

There are several limitations of the current study. We did not account for family history of RD in our analysis due to insufficient parental information. Although the measures of reading skill outcomes were age-appropriate and age-adjusted, they were assessed over a

two-year period important to reading development, which may have had some residual impact on our findings. In addition, the relationship between smoking and specific subtypes of readers (e.g., poor comprehenders) at the tail end of the reading distribution should be investigated further as data become available. There is the potential for misclassification of the exposure, as the smoking exposure variables were based on self-reported data. The assumption of uniform distribution of maximum amount of prenatal exposure to nicotine throughout the pregnancy may be an overestimation; however, we believe that the smoking data available in the ALSPAC reflect an accurate record because the information was collected in the pre/perinatal period. In addition, even though the current study focuses on the impact of prenatal nicotine exposure, cigarette smoke is composed of a large number of non-nicotine components. Nicotine, however, is a key substance in cigarette smoke that strongly affects brain development. The covariates on literacy and verbal-based interaction terms may not directly reflect measures of mother-child interaction (social-emotional basis of literacy development) or measures of the home literacy environment. Furthermore, due to the limitations of the current study design, we cannot make conclusions about causality. The current analysis does not include consideration of genetic factors with respect to smoking, although this is under investigation.

In conclusion, our findings demonstrate a negative association between high prenatal exposure to nicotine and reading skills in school-aged children. These findings suggest one risk factor for impaired reading that operates early in development. Further research is necessary not only to examine the effects of unmeasured confounders and the long-term effects of maternal smoking on reading outcomes on children, but also to extend our investigation to genetic studies of RD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table II

Distribution of children in each category of confounders included in the final model across the three nicotine exposure groups (n=5,119). Values are either proportions or means (SD).

	Prenatal nicotine exposure			
	None	**Low**	**High**	**Overall**
Sex				
Male	48.5	52.3	48.7	48.8
Female	51.5	47.7	51.3	51.2
Ethnicity *				
White	96.9	94.1	94.9	96.4
Non-white	3.1	5.9	5.1	3.6
Type of school child attends				
Primary	91.9	92.9	97.7	92.2
Private	5.9	4.8	1.6	5.6
Other	2.2	2.3	0.8	2.2
Literacy based interaction *				
High	47.1	42.8	35.8	46.3
Moderate	45.9	47.1	54.1	46.2
Low	7.1	10.1	10.1	7.5
Verbal based interaction				
High	65.3	67.1	66.1	65.6
Moderate	30.2	27.4	27.4	29.8
Low	4.5	5.1	6.5	4.6
ADHD				
Yes	1.4	2.4	1.6	1.5
Gestational age				
≥37wks	95.4	94.9	95.3	95.3
≤36wks	4.6	5.2	4.7	4.8
Marital status *				
Married	87	70.1	61.3	84.1
Social class - Maternal *				
Manual	11.9	23.9	37.5	14.1
Non-manual	88.1	76.1	62.5	85.9
Antenatal class attendance *	68.2	66.9	51	67.4
Alcohol consumption *				
Never	45.1	36.2	32.9	43.6
<1 glass PWK	41	40	38.4	40.7
1+ glasses PWK	12.8	20.2	22.6	14.1
1+ glasses PDAY	1.1	3.6	6.2	1.6
Resuscitation	8.3	7.3	6	8
Birth weight gm *	3467.1 (507.4)	3343.5 (533.6)	3294.4 (511.3)	3443.2 (516.7)

	Prenatal nicotine exposure			
	None	**Low**	**High**	**Overall**
Mother's age at delivery *	29.7 (4.3)	28.0 (4.9)	27.4 (5.1)	29.4 (4.5)
Phonology	20.9 (9.2)	20.6 (8.8)	19.2 (9.3)	20.8 (9.1)
Total IQ *	107.4 (15.0)	104.4 (14.3)	99.9 (13.8)	106.7 (15.0)

* Indicates χ^2 p value < .05 from univariable analyses of each covariate and prenatal nicotine exposure outcome.

Table V

Summary results of final adjusted analyses of maternal prenatal exposure to nicotine and reading skill outcomes.

	Final				
	1:Low		2:High		Overall
	Beta	*p*	Beta	*p*	*p*
Reading speed	−1.1	0.08	−3.0	0.03	0.03
Single-word identification	−0.6	0.08	−2.0	0.01	0.01
Spelling	−0.06	0.1	−0.3	0.001	0.002
Accuracy	−1.5	0.01	−5.2	<.0001	<.0001
Real words reading	−0.1	0.2	−0.8	0.0004	0.001
Nonword reading	−0.03	0.8	−0.4	0.2	0.4
Comprehension	−1.7	0.005	−4.6	0.0003	<.0001

Linear regression coefficients (Beta) and *P* values are presented. The non-smoking category is the reference group for nicotine exposure.

Table VI

Mean values for seven reading skill outcomes by nicotine exposure category and dichotomized phonology.

Prenatal nicotine exposure	**None**		**Low**		**High**	
Phonology	**Low**	**High**	**Low**	**High**	**Low**	**High**
Reading speed	102.8	111.7	101.2	110.1	96.1	107.2
Single-word identification	24.9	34.5	23.9	33.9	20.4	32.8
Spelling	−0.3	0.6	−0.4	0.5	−0.8	0.4
Accuracy	99.8	113.1	97.9	111.3	92.7	108.4
Real words reading	6.9	8.9	6.7	8.7	5.6	8.5
Nonword reading	4.5	6.5	4.4	6.7	3.8	6.4
Comprehension	98	107.1	95.9	105.2	91.1	102