

## REGULAR ARTICLE

# Familial confounding affected the associations between maternal smoking during pregnancy and offspring speech and language, scholastic and coordination disorders

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## Abstract

**Aim:** This study examined the associations between prenatal smoking and speech and language, scholastic, coordination and mixed developmental disorders in offspring, using sibling and population controls.

**Methods:** National Finnish registers were used to identify all 690 654 singletons born between 1996 and 2007 and any cases diagnosed with speech and language, scholastic, coordination and mixed developmental disorders by the end of 2012. Cases were compared to population controls, biological full-siblings and maternal half-siblings born during the same period. Conditional logistic regression was used to assess any associations between smoking during pregnancy and the selected developmental disorders.

**Results:** Prenatal smoking was higher in the mothers of the 27 297 cases (21.7%) than the 99 876 population controls (14.5%). The adjusted odds ratio for smoking throughout pregnancy, and any diagnosis of speech and language, scholastic, coordination or mixed developmental disorders, was 1.29 (95% confidence interval 1.24–1.34). However, when we compared a subsample of 15 406 cases and their 20 657 siblings, the association was no longer statistically significant (odds ratio 1.09, 95% confidence interval 0.98–1.21).

**Conclusion:** The sibling comparisons suggested that the associations between prenatal smoking and speech and language, scholastic, coordination and mixed developmental disorders were confounded by familial factors shared by differentially exposed siblings.

## KEYWORDS

developmental coordination disorder, learning disorders, siblings, smoking during pregnancy, specific language disorder

**Abbreviations:** aOR, adjusted odds ratio; CI, confidence interval; ICD, International Classification of Diseases; OR, odds ratio.

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## 1 | INTRODUCTION

The lifetime population prevalence rates for developmental disorders of speech and language, coordination and scholastic skills, namely specific learning disorders related to reading, writing and maths, are 6–15%.<sup>1–3</sup> Mixed developmental disorders refer to various combinations of these three disorders, in which none outweigh the others as the prime diagnosis.<sup>4</sup> Speech and language, scholastic and coordination disorders have been associated with both genetic and environmental risk factors, including prenatal smoking, and they are approximately twice as common in boys.<sup>5–9</sup> The self-reported prevalence for smoking during pregnancy is 7–17% in the Nordic countries and most of the expectant mothers who smoke in the first trimester continue to do so throughout pregnancy.<sup>10</sup> However, the causal nature of the association between smoking and learning-related adversities has been debated, because smoking is prone to unmeasured familial confounding.<sup>11</sup> This term refers to confounding induced by shared familial risk factors, including genetic factors, which are either difficult, or impossible, to account for using statistical adjustments for measured confounders.<sup>12</sup>

A limited number of studies have examined smoking during pregnancy as a risk marker for speech and language, scholastic or coordination disorders in offspring. Most studies have found no association with speech and language disorders,<sup>9</sup> but positive associations have been found for specific learning disorders and poor reading skills.<sup>7,13</sup> A systematic review<sup>14</sup> reported inconclusive results for coordination disorder. In addition, a cohort study<sup>15</sup> that measured maternal serum cotinine levels during pregnancy did not find that elevated cotinine levels were associated with offspring coordination disorders. Two reviews<sup>16,17</sup> that examined related topics, namely academic achievement and general cognitive function, concluded that a causal relationship between prenatal tobacco exposure and these two outcomes was probable. An Icelandic cohort study further suggested associations between smoking during pregnancy and offspring academic achievement. These associations persisted from grades 4–10, when the children were 10–16 years of age.<sup>18,19</sup> However, two Swedish nationwide register studies did not find evidence of poorer academic performance<sup>20</sup> or intellectual performance<sup>21</sup> when they analysed siblings or cousins who were differentially exposed to smoking during pregnancy.

Previous studies have shown no clear consensus on the associations between prenatal smoking and speech and language, scholastic or coordination disorders. Furthermore, the possible effects of familial confounding have not been sufficiently addressed. That is why we conducted this national register-based study, which comprised all singleton children born between 1996 and 2007 in Finland. Our primary aim was to examine the associations between smoking during pregnancy and speech and language, scholastic, coordination and mixed developmental disorders in offspring. First, we examined the associations between prenatal smoking and the disorders in the population sample. Then, we compared diagnosed subjects to their

### Key Notes

- Finnish national register data were used to examine any associations between prenatal smoking and children diagnosed with selected developmental disorders by the end of 2012.
- We found a modest association between prenatal smoking and speech and language, scholastic and coordination disorders when cases were compared with unrelated population controls.
- However, there was no association between those factors when we compared differentially exposed siblings.

siblings who were, and were not, exposed to smoking during pregnancy. Based on previous studies, we hypothesised that we would find an association between prenatal smoking and speech and language, scholastic, coordination and mixed developmental disorders in offspring. We also believed that any association would be reduced when we compared subjects with their siblings.

## 2 | METHODS

This register study was based on a national nested case-control and case and sibling design, and it comprised all 690 654 singleton live births in Finland between 1996 and 2007. We were able to link the data from Finnish nationwide registers using the unique personal identification codes that are issued to all Finnish residents at birth or when they migrate to the country.

### 2.1 | National registers

The number of live-born singleton children was obtained from the Finnish Medical Birth Register, which contains information on all births in Finland since 1987. Data are collected on maternal background characteristics, health-related behaviours, diagnoses during pregnancy and delivery and neonatal outcomes. The clinical diagnoses and the dates when diagnoses were issued were obtained from the Care Register for Health Care. This register gathers information from all publicly funded specialised health services in Finland and has covered inpatients since 1967 and outpatients since 1998.

The recorded diagnoses were based on the International Classification of Diseases (ICD). The Care Register is commonly used in epidemiological research and its validity ranges from satisfactory to excellent.<sup>22</sup> The Birth Register and Care Register are both maintained by the National Institute for Health and Welfare. Statistics Finland provided data on maternal education and the Digital and Population Data Services Agency provided death and immigration data.

## 2.2 | Maternal smoking

Information on self-reported smoking during pregnancy was obtained from the Birth Register. This information is reported during antenatal care, by public health nurses working at publicly funded maternity clinics or by midwives at delivery hospitals. Since 1991, the reports have included whether the mother smoked during the first trimester of pregnancy and whether she continued smoking after that trimester.<sup>10</sup> The register did not record the number of cigarettes the pregnant woman or other family members smoked. The self-reported smoking variable can be considered fairly reliable. In a previous Finnish population-based study,<sup>23</sup> which partially included the same birth cohorts as the present study, 4.9% of self-reported non-smokers were identified as smokers, based on their serum cotinine levels. According to data from the Finnish National Institute for Health and Welfare,<sup>24</sup> 99.7% of pregnant women visit maternity clinics, which are free of charge.

## 2.3 | Identifying cases and population controls

The cases were children who visited Finnish specialised health care services and received the following diagnoses by the end of 2012. These were grouped together in the Tenth Revision of the ICD (ICD-10) as F80–83 and broken down into the following: speech and language disorders (F80), scholastic disorders (F81), coordination disorders (F82) and mixed developmental disorders (F83). The diagnosis of mixed developmental disorders is used when there is a major overlap by the specific developmental disorders of speech and language, scholastic skills and motor function, but none of the disorders is dominant enough to be classified as the prime diagnosis.<sup>4</sup>

We studied the disorders as a total group, as well as in mutually exclusive groups. These individual groups were just speech and language disorders, just scholastic disorders, just coordination disorders and a group that combined mixed developmental disorders or two or more of the included diagnostic classes. In Finland, speech and language, scholastic, coordination and mixed developmental disorders are typically diagnosed in outpatient clinics for paediatric neurology, child psychiatry or paediatrics following a primary care referral. The assessment is multi-professional and often includes standardised psychological tests. Detailed information on the diagnostic procedures has previously been published.<sup>25</sup> We excluded children with co-occurring intellectual disabilities (F70–79) and autism spectrum disorders (F84). This was because it is difficult to distinguish the specific disorders of speech and language, scholastic skills and coordination if a child has more comprehensive impairments. Each case was individually matched with four controls by gender and date of birth  $\pm$  30 days. The controls were singleton births who were living in Finland at the time of the matched case's diagnosis, but without any of the outcome diagnoses, intellectual disabilities or autism spectrum disorders.

## 2.4 | Covariates

We identified covariates associated with both maternal smoking during pregnancy and speech and language, scholastic or coordination disorders in previous studies.<sup>10,14,25</sup> Maternal age at the time of birth was divided into four categories: under 20 years of age, 20–34, 35–39 or 40 or more years. The mother's psychiatric history was dichotomously classified as yes or no. A mother had a psychiatric history if she had any diagnosis of a mental disorder, according to the specific ICD-10 codes F10–F99, excluding mental retardation F70–F79, or the older ICD-9 codes 291–316 or ICD-8 codes 291–308. Maternal education was divided into two categories. These were college education if they achieved a higher vocational diploma or university degree and no maternal college education if they completed secondary school at the age of 15 and, or, underwent vocational education and training but did not go on to higher education. Maternal education was documented at the time of their child's birth. If it was missing at that point, it was checked again in 2012. Parity was classified as no previous births or at least one. Birthweight was classified as small for gestational age if it was less than  $-2$  standard deviations (SD), appropriate for gestational age ( $-2$  SD to  $+2$  SD) and large for gestational age (more than  $+2$  SD). Gestational age was classified as less than 37 weeks or 37 weeks or more. The Apgar score at one minute was classified as 0–6 or 7–10. We obtained the data on maternal psychopathology from the Care Register, the data on education from Statistics Finland and the rest of the data from the Birth Register.

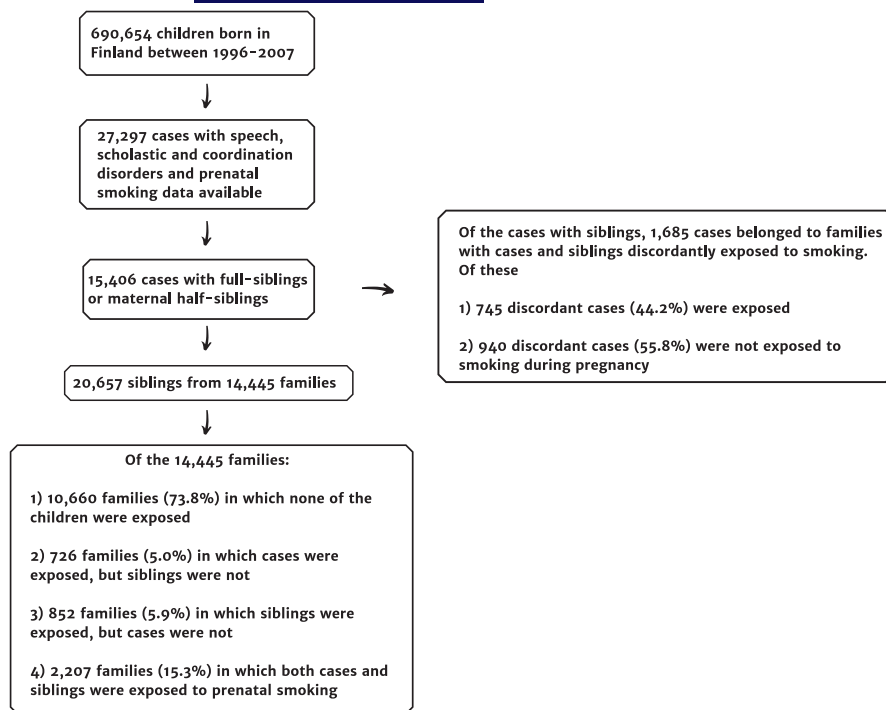
## 2.5 | Sibling controls

We included all biological full-siblings and maternal half-siblings from singleton births between 1996–2007 without an ICD-10 diagnosis of a speech and language, scholastic, coordination or mixed developmental disorder (F80–83). The sibling data set included perinatal birth information, for example the date of birth, information on prenatal smoking exposure and diagnoses from specialised services by the end of 2012. Siblings were only included if they were living in Finland at the time of the corresponding case's diagnosis and they did not have a diagnosed intellectual disability or autism spectrum disorder. The family clusters were divided into four different prenatal smoking exposure categories. These were as follows: cases and siblings who were both exposed to smoking, cases and siblings who were not exposed, cases but not siblings who were exposed and at least one sibling, but no case, exposed (Figure 1). We obtained the data on full-siblings and maternal half-siblings from the Birth and Care Registers and the Digital and Population Data Services Agency.

## 2.6 | Statistical analyses

Bivariate analyses were used to test the association between the covariates and prenatal smoking among the population controls,

FIGURE 1 Flow chart of the case and sibling subsamples



as well as any ICD-10 outcome diagnoses (F80–83). Conditional logistic regression was used to examine the association between prenatal smoking and case status. Smoking was examined as a three-class variable: smoking throughout pregnancy, only smoking in the first trimester and no smoking while pregnant. Separate analyses were conducted for the case-control sets for the aggregate group with any outcome disorder and the mutually exclusive groups of just speech disorders, scholastic disorders, coordination disorders and mixed developmental disorders or two or more disorders. First, unadjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Second, we produced adjusted ORs (aORs) for the selected covariates, by using multivariate conditional regression analysis.

The associations for prenatal smoking by subtype, namely speech and language, scholastic, coordination and mixed disorders, were similar, with overlapping confidence intervals. Because of that, and to increase the statistical power, we used the aggregate group with any outcome disorder for the sibling analyses. The cases and siblings were matched via the mother and the family clusters could include multiple cases and siblings. We used conditional logistic regression with fixed effects to test the within-family associations. The outcome was any ICD-10 diagnosis of speech and language, scholastic, coordination or mixed developmental disorder and the exposure was smoking during pregnancy. First, we computed the crude ORs, and then, we adjusted them for confounders that were not shared by the cases and siblings. These covariates included birth year, gender, parity, gestational age and birthweight for gestational age. The two-tailed statistical significance was  $p < 0.05$ , and the statistical analyses were performed with SAS statistical software version 9.4 (SAS Institute, North Carolina, USA).

## 2.7 | Ethics

The data from the registers were anonymised and handled according to Finnish data protection laws. No registered cases were contacted, which means that no informed consent was required. The data protection authorities gave us permission to use the registered data and The Ethics Committee of the Hospital District of Southwest Finland and the National Institute for Health and Welfare provided ethical approval for the study (registration number THL/1803/5.05.00/2013).

## 3 | RESULTS

Initially, 33 230 cases with speech and language, scholastic, coordination or mixed developmental disorders were identified from the Care Register. Of these, 5038 children with comorbid intellectual disabilities and, or, autism spectrum disorders were excluded. Data on smoking during pregnancy were available for 27 297 (96.8%) of the remaining 28 192 cases and 99 876 (93.7%) of the 106 616 matched population controls. Boys accounted for 71.2% and 70.4% of the samples, respectively. The median age at diagnosis was 5.6 years (interquartile range 4.0–7.1) for speech and language disorders, 8.9 (7.3–10.6) years for scholastic disorder, 5.6 (4.3–6.8) years for coordination disorder and 5.6 (3.9–7.2) for mixed developmental disorders. A number of covariates were included in the further analyses, because they were associated with both the outcome diagnoses and prenatal smoking in the control group. These were: maternal age, psychiatric history and education, parity and their offspring's gestational age and birthweight for gestational age (Table 1). The Apgar score at one minute did not show significant associations with smoking during pregnancy and was excluded.

TABLE 1 Potential covariates in relation to maternal smoking during pregnancy in the control group

	No smoking n = 85 374	Smoking only during the first trimester n = 2397	Smoking throughout pregnancy n = 12 105
	n (%)	n (%)	n (%)
Maternal age			
<20	1461 (1.7)	161 (6.7)	1021 (8.4)
20–34	67 612 (79.2)	1975 (82.4)	9413 (77.8)
35–39	13 296 (15.6)	219 (9.1)	1322 (10.9)
≥40	3005 (3.5)	42 (1.8)	349 (2.9)
Maternal psychiatric history			
No	75 840 (88.8)	1981 (82.6)	9300 (76.8)
Yes	9534 (11.2)	416 (17.4)	2805 (23.2)
Maternal education			
College education or higher	47 282 (55.4)	788 (32.9)	2193 (18.2)
No college education	38 092 (44.6)	1609 (67.1)	9912 (81.8)
Parity <sup>b</sup>			
0	34 273 (40.2)	1442 (60.2)	5287 (43.7)
≥1	51 043 (59.8)	955 (39.8)	6812 (56.3)
Gestational age <sup>c</sup>			
<37 weeks	3450 (4.1)	101 (4.2)	592 (4.9)
≥37 weeks	81 694 (95.9)	2288 (95.8)	11 469 (95.1)
Birthweight for gestational age <sup>d</sup>			
SGA <-2 SD	2058 (3.4)	77 (3.2)	628 (5.2)
AGA -2 SD - + 2 SD	80 199 (94.2)	2249 (94.1)	11 232 (93.2)
LGA > +2 SD	2848 (2.4)	63 (2.6)	197 (1.6)
Apgar score at one minute <sup>e</sup>			
0–6	3610 (4.2)	115 (4.8)	516 (4.3)
7–10	81 635 (95.8)	2278 (95.2)	11 574 (95.7)

Abbreviations: AGA, appropriate for gestational age; LGA, large for gestational age; SGA, small for gestational age.

All chi-square associations between the covariates and maternal smoking among controls were statistically significant ( $p < 0.001$ ), except for the Apgar score at one minute ( $p = 0.40$ ). All chi-square associations between covariates and speech, scholastic, coordination and mixed developmental disorders were statistically significant ( $p < 0.001$ ).

<sup>b</sup>Missing data for 64 controls and 15 cases

<sup>c</sup>Missing data for 282 controls and 65 cases

<sup>d</sup>Missing data for 225 controls and 83 cases

<sup>e</sup>Missing data for 148 controls and 54 cases

We found that 5937 of the 27 297 cases (21.5%) were exposed to smoking during pregnancy, compared to 14 502 of the 99 876 controls (14.5%). Of the 5937 mothers who smoked while pregnant with cases, 5235 (88.2%) smoked throughout their pregnancy and 702 (11.8%) only smoked during the first trimester. Just smoking during the first trimester did not show significant associations with any speech and language, scholastic, coordination or mixed disorder compared to not smoking after adjusting for confounders. The aOR for the total group with any outcome disorder was 1.02 (95% CI 0.93–1.11). The aORs for smoking throughout pregnancy were similar across the mutually exclusive subgroups of just speech and

language disorders, scholastic disorders, coordination disorders and mixed developmental disorder or more than two of the included disorders. The aOR range was 1.21–1.47 (Table 2). Because of the similarity of the findings across the subgroups, we used the aggregate group of any speech and language, scholastic, coordination or mixed disorder as the outcome in the sibling analyses.

Of the 27 297 diagnosed cases, 15 406 (56.4%) born to 14 445 mothers had siblings who were eligible to take part in the study (Figure 1). There were 20 657 siblings included in the study: 18 239 (88.3%) were full-siblings and 2418 (11.7%) were maternal half-siblings. The mean age of the cases was  $11.5 \pm 3.1$  years and the

TABLE 2 Associations between maternal smoking during pregnancy and different speech and language, scholastic, coordination and mixed disorder subtypes in the population-based sample, born in Finland between 1996–2007

	Cases n (%)	Controls n (%)	Crude OR (95% CI)	p value	Adjusted <sup>a</sup> OR (95% CI)	p value
Any of the disorders <sup>b</sup>						
No smoking	21 360 (78.3)	85 374 (85.5)	Reference		Reference	
Only during first trimester	702 (2.6)	2397 (2.4)	1.17 (1.08–1.28)	<0.001	1.02 (0.93–1.11)	0.87
Throughout pregnancy	5235 (19.2)	12 105 (12.1)	1.72 (1.66–1.78)	<0.001	1.29 (1.24–1.34)	<0.001
Speech and language disorder only						
No smoking	8665 (80.4)	34 039 (85.8)	Reference		Reference	
Only during first trimester	280 (2.6)	991 (2.5)	1.12 (0.98–1.28)	0.12	0.99 (0.86–1.14)	0.87
Throughout pregnancy	1838 (17.1)	4631 (11.7)	1.55 (1.46–1.64)	<0.001	1.21 (1.14–1.29)	<0.001
Scholastic disorder only						
No smoking	2875 (76.9)	11 900 (85.2)	Reference		Reference	
Only during first trimester	77 (2.1)	268 (1.9)	1.18 (0.91–1.53)	0.21	1.03 (0.79–1.35)	0.87
Throughout pregnancy	787 (21.1)	1798 (12.9)	1.81 (1.65–1.99)	<0.001	1.34 (1.22–1.49)	<0.001
Coordination disorder only						
No smoking	1989 (78.8)	8089 (85.6)	Reference		Reference	
Only during first trimester	80 (3.2)	246 (2.6)	1.32 (1.01–1.70)	0.05	1.19 (0.91–1.57)	0.34
Throughout pregnancy	456 (18.1)	1120 (11.9)	1.65 (1.47–1.86)	<0.001	1.47 (1.29–1.67)	<0.001
Mixed disorder or at least two disorders						
No smoking	7831 (76.4)	31 346 (85.2)	Reference		Reference	
Only during first trimester	265 (2.6)	892 (2.4)	1.19 (1.04–1.37)	0.02	1.02 (0.88–1.17)	0.87
Throughout pregnancy	2154 (21.0)	4556 (12.4)	1.89 (1.78–2.00)	<0.001	1.32 (1.24–1.40)	<0.001

Abbreviations: CI, confidence interval. ORs calculated with conditional logistic regression; OR, odds ratio.

All p-values were corrected for multiple hypothesis testing with the false discovery rate method.

<sup>a</sup>Adjusted for maternal age, psychiatric history and education, parity, gestational age and birthweight for gestational age.

<sup>b</sup>Any disorder of speech and language (F80), scholastic skills (F81), coordination (F82) or mixed developmental disorder (F83), as classified by the International Classification of Diseases, Tenth Revision.

mean age of their siblings was  $11.1 \pm 3.4$  years at the end of the follow-up period in December 2012. The gender distribution differed, as 71.7% of the cases were boys, compared to 49.0% of the siblings. We found that 2761 of the 15 406 cases (17.9%) and 3463 of the 20 657 eligible siblings (16.8%), were exposed to prenatal smoking throughout pregnancy (Table 3). The 14 445 families included 1578 (10.9%) where the cases and siblings did not have the same exposure. In the remaining families, all the children were exposed, or none were exposed (Figure 1). A modest association was found between smoking throughout pregnancy and any outcome disorder when we compared the diagnosed cases to the population controls (aOR 1.29, 95% CI 1.24–1.34). This was entirely attenuated when we compared the cases and their siblings (aOR 1.09, 95% CI 0.98–1.21) (Table 3).

## 4 | DISCUSSION

We found a modest association between prenatal smoking and speech and language, scholastic and coordination disorders in the population sample. However, the sibling analyses suggest that the

observed associations were explained by unmeasured familial confounding. These findings are novel, as no previous studies have examined speech and language, scholastic and coordination disorders in children and their non-affected siblings. The aOR for prenatal smoking and any of the outcome diagnoses was 1.29. This was similar, or a bit lower, to other studies that measured the association between smoking and parent-reported learning disabilities<sup>7</sup> or coordination disorders.<sup>14</sup> Our sibling analyses displayed no such associations, in common with previous studies that used sibling designs to explore academic performance or intelligence.<sup>11,20,21</sup>

Speech and language, scholastic and coordination disorders are considerably heritable. For example, the estimated heritability for reading disorders is 40–70%.<sup>26</sup> Smoking initiation and nicotine dependence display heritability estimates of 40–70%<sup>27</sup> and smoking has been shown to be genetically correlated with neurocognitive outcomes.<sup>28</sup> These genetic linkages could partly explain the associations this study found. The associations in the population sample might reflect mounting genetic risk factors of overlapping learning disorders and addictive behaviour. In addition, genetics is likely to play a role in the attenuation of the ORs when siblings are compared, as full-siblings share approximately 50% of their co-segregating

**TABLE 3** Associations between maternal smoking during pregnancy and speech and language, scholastic, coordination and mixed developmental disorders in the different samples, who were all born in Finland between 1996–2007

Full cohort	Case* sample n (%)	Comparison sample n (%)	Crude OR (95% CI)	p value	Adjusted OR (95% CI)	p value
	<b>All cases*</b> n = 27 297	<b>Population controls</b> n = 99 876				
No smoking	21 360 (78.3)	85 374 (85.5)	Reference		Reference	
Only during first trimester	702 (2.6)	2397 (2.4)	1.17 (1.08–1.28) <sup>a</sup>	<0.001	1.02 (0.93–1.11) <sup>b</sup>	0.87
Throughout pregnancy	5235 (19.2)	12 105 (12.1)	1.72 (1.66–1.78) <sup>a</sup>	<0.001	1.29 (1.24–1.34) <sup>b</sup>	<0.001
<b>Sibling subsample</b>	<b>Cases* with siblings</b> n = 15 406	<b>Maternal full and half-siblings</b> n = 20 657				
No smoking	12 291 (79.8)	16 747 (81.1)	Reference		Reference	
Only during first trimester	354 (2.3)	447 (2.2)	1.02 (0.84–1.20) <sup>c</sup>	0.88	1.00 (0.84–1.18) <sup>d</sup>	0.96
Throughout pregnancy	2761 (17.9)	3463 (16.8)	1.10 (0.99–1.21) <sup>c</sup>	0.10	1.09 (0.98–1.21) <sup>d</sup>	0.12

<sup>b</sup> Adjusted for maternal age, psychiatric history and education, parity, gestational age and birthweight for gestational age.

<sup>d</sup> Adjusted for gender, parity, birth year, gestational age and birthweight for gestational age.

\*Cases with speech and language, scholastic, coordination and mixed developmental disorders (ICD-10 F80–83). Abbreviations: CI, confidence interval; OR, odds ratio.

<sup>a,b</sup> Calculated using conditional logistic regression.

<sup>c,d</sup> Calculated using conditional logistic regression with fixed effects.

genes and half-siblings share 25%. Therefore, the sibling design partly controlled for genetic confounding.

Sibling comparisons are popular in epidemiological research, probably because they can minimise the confounding caused by the variables that siblings share. Nevertheless, sibling designs have some limitations. For example, measurement errors of exposure are more likely to attenuate the associations in sibling-paired analyses.<sup>29</sup> A previous Finnish population-based study demonstrated that self-reporting underestimated prenatal smoking by 4.9% when serum cotinine levels were used for confirmation.<sup>23</sup> As the present study was based on self-reporting, a similar proportion might have been misclassified and this may have somewhat attenuated the associations in both the population and sibling analyses. However, the major limitation of the sibling approach is that only the subset of mothers who manage to change their smoking habits from one pregnancy to another provided information for the estimates in the sibling analyses. Some sibling studies have expanded their comparisons to differently exposed cousins,<sup>20,30</sup> because they are more generalisable to the population. The results from cousin studies have been consistent with sibling studies. Our family sample comprised full-siblings and maternal half-siblings, but unfortunately no cousins. Including half-siblings attenuated the level of genetic confounding we were able to control for, because they only share 25% of their genes. Despite this limitation, we found that the association was entirely confounded.

The main strengths of this study included the nationwide sample of diagnosed speech and language, scholastic, coordination and mixed developmental disorders. We also used data based on ICD-10, which is a uniform and reliable diagnostic system. The large sample size meant that we could study specific disorders independently. In addition, we were able to adjust for several measured confounders, as well as unmeasured familial confounders in the sibling analyses. However, there were also some limitations. First, the study only included diagnoses from specialised services, which means we could have missed cases with speech and language, scholastic, coordination and mixed developmental disorders that never got that far. However, children are screened during free health check-ups in Finnish primary care and both primary and specialised health services are publicly funded. This suggests that few cases would have been missed due to lack of access to health services. Moreover, the ratio of smoking versus non-smoking mothers using the services was estimated to reflect the population in general. Second, we did not have information on the daily cigarette consumption of the pregnant mothers, the smoking habits of the fathers or potential exposure to second-hand smoke.

## 5 | CONCLUSION

This study found a modest association between prenatal smoking and speech and language, scholastic and coordination disorders when we compared cases with unrelated population controls, but not differentially exposed siblings. Our results suggest that the associations found between prenatal smoking and developmental disorders

of learning and coordination in previous studies were probably due to residual confounding of shared familial factors, including genetic factors. Future genetically informed biomarker studies on the topic are needed to confirm the findings. Furthermore, our findings highlight the importance of research into the causal environmental risk factors for developmental disorders, which could provide targets for preventive interventions. The advice remains that women should not smoke during pregnancy, because of the numerous adverse birth-related outcomes that have been identified in rigorously controlled studies, including preterm birth and low birthweight.

## CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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