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# Congenital cerebral palsy and prenatal exposure to self-reported maternal infections, fever, or smoking

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## Abstract

**OBJECTIVE—**The objective of the study was to investigate the association between maternal self-reported infections, fever, and smoking in the prenatal period and the subsequent risk for congenital cerebral palsy (CP).

**STUDY DESIGN—**We included the 81,066 mothers of singletons born between 1996 and 2003 who participated in the Danish National Birth Cohort. Children were followed up through December 2008. Information on maternal infections, fever, smoking, and other demographic and lifestyle factors during pregnancy were reported by mothers in computer-assisted telephone interviews in early and midgestation. We identified 139 CP cases including 121 cases of spastic CP (sCP) as confirmed by the Danish National Cerebral Palsy Register. Cox proportional hazards regression models were used to estimate adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs).

**RESULTS—**Self-reported vaginal infections were associated with an increased risk of CP and sCP (aHR, 1.52; 95% CI, 1.04–2.24; and aHR, 1.73; 95% CI, 1.16–2.60, respectively) and particularly untreated vaginal infections were associated with an increased risk of sCP (aHR, 1.95; 95% CI, 1.16–3.26). Fever was associated with the risk of CP (aHR, 1.53; 95% CI, 1.06–2.21). Smoking 10 or more cigarettes per day during pregnancy was also associated with sCP (aHR, 1.80; 95% CI, 1.10–2.94). There was a modest excess in risk for children exposed to both heavy

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smoking and vaginal infections. No other self-reported infections were significantly associated with CP.

**CONCLUSION—**Self-reported vaginal infections, fever, and smoking 10 or more cigarettes per day during pregnancy were associated with a higher risk of overall CP and/or sCP.

## Keywords

congenital cerebral palsy; maternal infections; pregnancy; smoking

Congenital cerebral palsy (CP) constitutes a group of permanent disorders of movement and posture causing activity limitation attributed to non-progressive disturbances that occurred in the developing fetal or infant brain.[1] CP is the most common physical developmental disability in childhood with a birth prevalence of 2 per 1000 live births in Denmark.[2,3] The incidence of CP increases with lower gestational age, up to 100 cases per 1000 births in extreme preterm cases (<28 weeks).[4,5] Improvements in perinatal care and neonatal survival in recent decades have increased the survival of children born preterm and therefore the number of CP cases.[4,6]

Maternal fever[7,8] and maternal infections[9–11] have been associated with an increased risk of CP, irrespective of gestational age. Infections of the vagina or urinary tract during pregnancy have been of special interest because of their proximity to the fetus, but most studies have not clearly separated these infections. Self-reported data from questionnaires administered during pregnancy provide separation of each type of infection and more importantly include infections that did not receive medical attention. The proposed mechanism of action for maternal infections increasing risk of CP is by triggering a fetal inflammatory response, which results in fetal brain damage, particularly if added to fetal hypoxia.[12]

Smoking 10 or more cigarettes during pregnancy has also been associated with CP.[13] The possible mechanism of action of this association is by the creation of a pathological hypoxic environment for the fetus.[13] Moreover, smoking has also been associated with vaginal infections.[14] We therefore hypothesize that exposure both maternal infection and maternal smoking may result in excess risk of CP in comparison with either exposure alone.

Maternal age,[15–17] smoking during pregnancy,[14,18] alcohol consumption,[14,19] socioeconomic status,[20–22] household size during pregnancy,[14,22] season of pregnancy start,[23,24] and calendar year of birth[2,25] may confound the association between infection and CP. These factors have been shown to be associated with an increased risk of CP as well as being associated with increased risk of infections.

This study explores the association between CP and self-reported maternal infections during pregnancy, using the Danish National Birth Cohort and the Danish National Cerebral Palsy Registry. We analyzed all infections combined and separately as well as fever (a marker of infection). We specifically focused on the association between CP and self-reported vaginal infections, urinary tract infections, or smoking, adjusting for available confounders. Because there might be specific etiological links between infection and spastic CP (sCP),[26] we analyzed this group separately.

## Materials and Methods

The Danish National Birth Cohort is a nationwide population-based cohort of pregnancies and their offspring designed to provide questionnaires for collecting self-reported data for epidemiological studies of short-term and long-term consequences of intrauterine exposures. Details on the Danish National Birth Cohort study design and recruitment procedures have been published elsewhere, [27] and the translated questionnaires are available (www.dnbc.dk).

We included women in our study only if they participated in both of the 2 interviews during pregnancy (n = 83,935). We additionally excluded 2447 non-singleton children, 261 children who died, and 118 children who emigrated prior to their first birthday, and 43 children who were not in the Danish Medical Birth Registry. Of the 261 children who died, 186 died neonatally (within the first 30 days after delivery). This study was approved by the Danish Data Protection Agency. The study was also approved and by the Research Ethic Committee and University of California, Los Angeles, Institutional Review Boards.

Danish National Birth Cohort participants were identified as having validated CP if they were alive after the first year of life and included in the Danish Cerebral Palsy Registry. Validation of CP cases and inclusion in the register has been previously described.[28] Time of CP onset for the analysis was defined as age 1 year or first recorded date of diagnosis in the Danish Cerebral Palsy Registry. If a child's date of diagnosis was prior to the age of 1 year (n = 76), the child's date of diagnosis was recentered to the date of child's first birthday (date of birth plus 365 days) and coded as a CP child if included in the CP registry. All children were followed up from 1 year of age until a reported diagnosis of CP in the Danish Cerebral Palsy Registry, death, or Dec. 31, 2008, whichever occurred first.

Information on urinary tract infections (cystitis, pyelonephritis), vaginal infections, diarrhea, cough, genital herpes, venereal warts, herpes labialis, fever, and smoking was collected from participants as part of the Danish National Birth Cohort interviews.

Because the etiology of CP is largely unknown, confounding adjustment is based on availability of data and previous findings. Information on maternal age at birth and calendar year of birth was obtained from the Danish Medical Birth Registry, whereas information on other confounders (smoking during pregnancy, alcohol consumption, socioeconomic status, household size during pregnancy) was available from interviews.

Coding of social status was based on highest self-reported education and job titles between both parents at the time of recruitment. Parents who had a completed education 4 years beyond secondary school education or were in management were classified as high social status. Parents with middle-range training and skilled workers were classified as middle social status, and unskilled workers and unemployed were classified as low social status. If unemployed more than 12 months, parents were categorized in the lowest category, if unemployed less than 12 months, parents' completed education and or training were used to determine status.

Women were classified into alcohol consumption categories based on the maximum consumption at any point in time during their pregnancy, as described in either of the 2

interviews. Binge drinking was having at least 1 episode of intake of 5 drinks or more in 1 night during pregnancy. In addition to potential confounders, we collected information concerning gestational age (in weeks) at birth, and Apgar score at 5 minutes from the Danish Medical Birth Registry.

Characteristics of maternal cohort across maternal infection and smoking groups were summarized as proportions and analyzed using $\chi^2$ tests. For each infectious exposure group, we modeled the risk of CP and the risk of sCP. Hazard ratios and 95% confidence intervals (CIs) were estimated by Cox proportional hazard regression models with person-years as the time-to-event variable using robust sandwich covariance estimates to take into account interdependency among women who had more than 1 child during the cohort recruitment time and therefore participated more than once in the cohort (4997 women participated in the cohort twice and 56 women participated 3 times). Adjusted hazard ratios included all potential confounders listed above. Confounders were selected for adjustment in CP and sCP models a priori based on literature review.

Multiple imputation methods were used to replace missing covariate data. The procedure generated 5 different simulated completed datasets, replacing each missing value with a set of plausible values based on the other available values for that variable. The multiply imputed data sets were then analyzed by using standard procedures for complete data and combining the results from these analyses. Missing values requiring imputation included: socioeconomic status (n = 300), household size (n = 77), season of pregnancy start (n = 217), alcohol (n = 413), binge drinking (n = 1233), smoking (n = 671), and gestational age (n = 217).

Interactions on a multiplicative scale were tested by creating 4 groups of exposure: no exposure to either factor, exposure to 1 factor (or the other), and exposure to both factors. Only children in any of the 4 groups were included in the analysis. Those with missing data in either factor of a pair were not included in the analyses. The group of no exposure to either factor was used as a reference group in the analysis.

We also performed analyses by stratification on gestational age (preterm defined as <37 weeks, and term defined as ≥37 weeks) and by Apgar score (<10 and 10) to test whether the results were independent of these as intermediate variables. Sensitivity analyses for multiple imputation methods were also conducted by retesting the associations using complete case analyses and for eliminating the possibility of recall bias by excluding mothers with interviews conducted postpartum. Plots of log (-log [survival rate]) against log (survival time) were used to check the proportionality assumption. All analysis was carried out in SAS version 9.2 (SAS Institute, Cary, NC).[29]

## Results

All together, 81,066 singletons were included in the analysis. Children were followed up to a maximum of 11.4 years, and the mean length of follow-up time was 7.2 ± 1.5 years (mean ± SD), respectively. A total of 139 children were identified as having CP, of which 121 had sCP. The characteristics of the maternal cohort by factors associated significantly with CP or

sCP (vaginal infections, fever, and smoking) are presented in Table 1. Characteristics of mothers of the exposed and unexposed children were rather similar. Mothers who smoked heavily were more likely to having binged and less likely to be of higher socioeconomic status.

The associations between infections, fever, and smoking with CP and sCP are shown in Table 2. The risk of delivering an infant with CP overall or sCP specifically was not significantly different for women reporting any infection compared with women not reporting any infection. When the data were analyzed according to the type of infection, there was an association between vaginal infections and both overall CP and sCP risk but no significant associations with other infections. When vaginal infections were separated into untreated and treated groups, a significant association was noted for untreated vaginal infections and sCP.

There was no significant association of urinary tract infections with either CP or sCP. Maternal fever was significantly associated with having a child with CP overall but not sCP alone, although the association was in the same direction (Table 2). We analyzed separately vaginal infection and urinary tract infection for association with sCP in patients who did not report both infections. There were 29 women who had vaginal infections with no reported urinary infections and had a child with sCP (adjusted hazard ratio [aHR], 1.60, 95% confidence interval [CI], 1.04–2.47) and 4 women who reported urinary infections but did not report a vaginal infection and had a child with sCP (aHR, 0.48, 95% CI, 0.18–1.32).

We observed a significant association between heavy maternal smoking (more than 10 cigarettes per day) during pregnancy and risk of sCP but no significant association for moderate smoking.

Tables 3 and 4 present interactions between significant findings in our study. The interaction for vaginal infections and heavy smoking was analyzed for sCP (Table 3), and the interaction for fever with vaginal infections was analyzed for overall CP (Table 4). There were no deviations from the multiplicative model for the interaction of fever with vaginal infection in overall CP. However, the interaction for untreated vaginal infections with heavy smoking showed a slight excess from the multiplicative model.

There were only 3176 preterm births in our cohort and they accounted for 32 cases of CP and 29 cases of sCP. In children born at term, vaginal infections and heavy smoking were significantly associated with the outcome sCP (aHR, 1.70; 95% CI, 1.08–2.67; and aHR, 1.79; 95% CI, 1.02–3.15, respectively). Additionally, the association of CP with maternal fever was also significant in children born at term (aHR, 1.63; 95% CI, 1.09–2.44). These 3 associations were not statistically significant in children born preterm (aHR, 1.59; 95% CI, 0.51–4.94; aHR, 1.70; 95% CI, 0.71–4.06; aHR, 0.93; 95% CI, 0.35–2.49, respectively).

We additionally stratified by Apgar score (10 or <10) (Tables 5 and 6). For births that had a normal Apgar score of 10 (n=74,506, 93%), the associations of fever and heavy smoking with overall CP as well as the association between heavy smoking and sCP were significantly positive and even higher than in the total group, whereas in births with Apgar score less than 10 (n = 5957, 7%), the point estimates were close to 1, and associations were

not statistically significant. Conversely, the association of untreated vaginal infection with sCP was significant only in children with Apgar less than 10 with a marked increase in point estimate.

Sensitivity analyses comparing our study results to complete case analyses and analysis excluding mothers with interviews conducted postpartum are presented in Table 7.

In 619 births, mothers were interviewed after the child was delivered. After excluding these children from the analysis, results were similar to those in the study. Furthermore, results were similar when using complete case analyses in place of imputation methods.

## Comment

After adjustment for available potential confounders maternal report of prenatal fever, heavy smoking, and vaginal infections were significantly associated with an increased risk of CP. All vaginal infections and fever were associated with overall CP. All vaginal infections, untreated vaginal infections, and heavy smoking were associated with sCP. This suggests that there may be differences between risk factors for spastic versus nonspastic CP. The association of vaginal infections and heavy smoking with sCP occurred in term birth, eliminating the possibility that they entirely were due to their association with preterm birth.

We additionally conducted a stratified analysis by Apgar score. The stratification by Apgar score showed that vaginal infection, particularly untreated vaginal infections, were strongly associated with sCP in children with a suboptimal Apgar score (<10) at 5 minutes after delivery. This indicates that fetal distress expressed as a lower Apgar score is either an intermediate or effect modifier in the association between vaginal infection and sCP.

Our data also showed that sCP was associated with untreated but not with treated vaginal infections. The cohort size was, however, too small to ascertain that successful treatment accounts for this finding.

In our study, questions were asked specifically about vaginal infections and urinary tract infections separately in a way that it is unlikely that women would confuse one with the other. In previous studies showing association between urogenital infections and CP, vaginal infections were not separated from other infections of the urogenital tract.[30–33] The strength of our study is that we were able to address separately self-reported untreated vaginal infections, treated vaginal infections and urinary infections. Furthermore, all data are prospectively collected prior to the outcome CP.

In this study we showed fever to be associated with CP, but we did not separate fever from infection vs other sources of hyperthermia such as using a solarium or sauna. It is, however, unlikely women will classify elevated body temperature due to these exposures as fever. Hyperthermia during pregnancy has been associated with other neurological disorders in children,[7,34–37] but some reports were limited to perinatal fever.[7,8,34,35]

Our results suggest that heavy rather than low to moderate smoking is responsible for the association between smoking and CP, but we do not have sufficient data to rule out an

association between moderate smoking and CP. A large case-control study found an association between CP and smoking in pregnancy[16] but did not report associations by level of smoking. Maternal smoking during pregnancy is associated with placental malformation and malfunction, [13] fetal growth restriction[38] and preterm deliveries.[39] Smoking effect may be mediated by these factors.

In the group of children that were exposed to smoking and vaginal infection, we noted a slight deviation from the multiplicative model, which led to a modest excess of risk of sCP for those exposed to both. It is conceivable that a placenta abnormality caused by heavy smoking is creating a hypoxic environment, [13] which exacerbates the detrimental effects of the presumed fetal inflammatory response induced by infection. However, this association demonstrated a modest excess in risk is based on small numbers. Replication in larger datasets is warranted.

Urinary tract infections, as defined for this analysis, were not associated with an increased risk of CP. We cannot, however, rule out that severe urinary tract infection requiring antibiotic treatments or hospitalizations are a risk factor for CP. A large recent analysis did not find a statistically significant association of urinary tract infections and CP.[40] A case-control study showed urinary tract infections to be associated with CP[41] but was subject to differential recall bias because it used retrospective interviews after CP diagnosis.

A strength of our study is that our data are most likely free of differential recall bias because exposures were all self-reported prior to the diagnosis of CP, and sensitivity analyses excluding the births in which interviews were conducted after delivery further showed similar results. An additional strength of our study is the inclusion of cases believed by the patient not to require medical attention. In addition, our data are using the Danish National Cerebral Palsy Register, which includes only cases confirmed by expert reviews.

Limitations of our study include the fact that our data on infections were self-reported and limited to those addressed in the interviews and could therefore not differentiate fungal from bacterial vaginal infections. Also, because maternal infection reports could not be confirmed, nondifferential misclassification of exposure is possible and likely. The population studied was relatively homogeneous, and our data should be confirmed in populations with other ethnic groups.

We used multiple imputation methods to fill in missing values to maximize the number of observations used in each analysis, which may have led to some loss of precision in the estimates. However, sensitivity analysis using complete cases without missing data resulted in similar associations. Because we used only women who completed both interviews, we could not ascertain that the women who missed only 1 interview were missing at random.

Additionally, because point estimates were never larger than 2, even when significant and confidence intervals were wide, most likely due to small numbers, these associations should be replicated in other and larger databases to corroborate our findings. Although data were available for a large number of confounders in our cohort, we were able to adjust only for identified confounders with available data, and we cannot exclude the possibility of residual

confounding. Moreover, because this an observational cohort study, we cannot assume that associations imply causal relationships.

In summary, our study adds support to the fact that maternal vaginal infection, maternal fever, and maternal smoking, during early and mid pregnancy, are associated with increased risks of CP and/or sCP in the child. Whether this is related to the infection itself or changes in the immune system in not known.[42]

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**TABLE 1**

Characteristics of maternal cohort according to selected self-reported maternal infections and smoking

| | Vaginal infections | | Fever | | Smoking | | | |
|---|---|---|---|---|---|---|---|---|
| **Covariate** | **No** | **Yes** | **No** | **Yes** | **No** | **1–9 cigarettes per day** | **≥10 cigarettes per day** | **All subjects** |
| n | 62,788 | 16,719 | 56,493 | 24,744 | 59,285 | 10,768 | 10,342 | 81,066 |
| Maternal age, y | | | | | | | | |
| 15–24 | 9.4 | 8.7 | 9.2 | 9.5 | 7.3 | 12.7 | 17.0 | 9.3 |
| 25–29 | 39.1 | 37.4 | 39.1 | 37.9 | 38.8 | 40.0 | 36.7 | 38.7 |
| 30–34 | 37.1 | 38.2 | 36.8 | 38.4 | 38.8 | 34.4 | 31.6 | 37.3 |
| ≥35 | 14.4 | 15.7 | 14.9 | 14.2 | 15.1 | 12.9 | 14.7 | 14.7 |
| Socioeconomic status | | | | | | | | |
| High | 66.6 | 68.7 | 66.4 | 68.3 | 71.7 | 62.1 | 45.3 | 67.0 |
| Middle | 29.5 | 27.7 | 29.7 | 27.9 | 25.7 | 33.4 | 44.5 | 29.1 |
| Low | 3.9 | 3.6 | 3.9 | 3.8 | 2.6 | 4.5 | 10.2 | 3.9 |
| Household size during pregnancy | | | | | | | | |
| 1 person | 1.1 | 1.4 | 1.1 | 1.2 | 0.7 | 1.9 | 2.6 | 1.2 |
| 2 persons | 45.5 | 39.5 | 46.4 | 38.8 | 43.6 | 48.7 | 43.4 | 44.3 |
| 3 persons | 36.9 | 39.3 | 35.6 | 41.8 | 38.4 | 35.1 | 33.9 | 37.3 |
| ≥4 persons | 16.5 | 19.8 | 16.9 | 18.2 | 17.3 | 14.3 | 20.1 | 17.2 |
| Season pregnancy started | | | | | | | | |
| Fall | 26.8 | 26.0 | 24.9 | 31.0 | 26.7 | 26.8 | 26.1 | 26.6 |
| Winter | 23.5 | 23.6 | 25.0 | 19.9 | 23.4 | 23.4 | 24.3 | 23.5 |

| Covariate | Vaginal infections | | Fever | | Smoking | | | All subjects |
|---|---|---|---|---|---|---|---|---|
| | No | Yes | No | Yes | No | 1–9 cigarettes per day | ≥10 cigarettes per day | |
| Spring | 24.6 | 25.0 | 26.8 | 19.5 | 24.5 | 25.1 | 25.6 | 24.8 |
| Summer | 25.1 | 25.4 | 23.3 | 29.6 | 25.4 | 24.7 | 24.0 | 25.2 |
| Birth year | | | | | | | | |
| 1996–1999 | 34.7 | 33.8 | 33.9 | 35.7 | 33.9 | 35.5 | 36.6 | 34.3 |
| 2000–2003 | 65.3 | 66.2 | 66.1 | 64.3 | 66.1 | 64.5 | 63.4 | 65.7 |
| Maternal smoking | | | | | | | | |
| None | 73.9 | 73.2 | 74.4 | 72.2 | — | — | — | 73.7 |
| 1–9 cigarettes/d (moderate) | 13.3 | 13.7 | 13.2 | 13.9 | — | — | — | 13.4 |
| >10 cigarettes/d (heavy) | 12.8 | 13.1 | 12.4 | 13.9 | — | — | — | 12.9 |
| Maternal alcohol | | | | | | | | |
| None | 42.7 | 39.9 | 42.1 | 42.2 | 41.0 | 40.1 | 50.0 | 41.9 |
| Light (≤1 drinks/wk) | 34.8 | 35.5 | 35.0 | 35.0 | 36.3 | 34.0 | 28.3 | 35.1 |
| Moderate (2–4 drinks/wk) | 20.5 | 22.3 | 20.9 | 20.8 | 21.0 | 23.4 | 18.1 | 20.9 |
| Heavy (≥5 drinks/wk) | 2.0 | 2.3 | 2.0 | 2.0 | 1.7 | 2.5 | 3.6 | 2.1 |
| Any episode of binge drinking ≥5 drinks in 1 night | 30.4 | 32.3 | 30.5 | 31.4 | 27.1 | 42.8 | 39.7 | 30.8 |

Data shown as percentages.

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**TABLE 2**

HRs for CP according to infections and smoking

| | All CP (n = 139) | | | | | | | Spastic CP (n = 121) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Number | | | | | | | Number | | | | |
| | Non-CP | | CP | | | | | Spastic CP | | | | |
| **Factors** | **Unexposed** | **Exposed** | **Unexposed** | **Exposed** | **Crude HR** | **aHR[a]** | **95% CI** | **Unexposed** | **Exposed** | **Crude HR** | **aHR[a]** | **95% CI** |
| All infections | 30,097 | 45,126 | 48 | 71 | 0.99 | 0.98 | 0.68–1.41 | 41 | 62 | 1.01 | 1.00 | 0.67–1.48 |
| Vaginal infections (all) | 62,695 | 16,682 | 93 | 37 | 1.50 | 1.52 | 1.04–2.24 | 77 | 35 | 1.71 | 1.73 | 1.16–2.60 |
| Untreated | 71,798 | 7579 | 112 | 18 | 1.60 | 1.62 | 0.98–2.69 | 94 | 18 | 1.93 | 1.95 | 1.16–3.26 |
| Treated | 70,274 | 9103 | 111 | 19 | 1.41 | 1.44 | 0.88–2.37 | 95 | 17 | 1.52 | 1.55 | 0.91–2.64 |
| Urinary infections | 70,732 | 9191 | 116 | 11 | 0.73 | 0.74 | 0.40–1.38 | 100 | 10 | 0.77 | 0.79 | 0.41–1.50 |
| Cystitis | 67,937 | 9073 | 112 | 11 | 0.74 | 0.74 | 0.40–1.38 | 96 | 10 | 0.78 | 0.79 | 0.41–1.51 |
| Pyelonephritis | 79,496 | 291 | 125 | 1 | 2.19 | 2.29 | 0.32–16.45 | 108 | 1 | 2.53 | 2.56 | 0.35–18.51 |
| Diarrhea | 61,160 | 18,790 | 98 | 32 | 1.06 | 1.03 | 0.69–1.54 | 84 | 28 | 1.09 | 1.04 | 0.68–1.59 |
| Cough | 67,406 | 12,819 | 107 | 23 | 1.13 | 1.11 | 0.71–1.75 | 92 | 20 | 1.14 | 1.11 | 0.69–1.81 |
| Herpes labialis | 70,029 | 10,005 | 117 | 11 | 0.66 | 0.66 | 0.35–1.22 | 101 | 9 | 0.62 | 0.62 | 0.32–1.24 |
| Genital herpes | 78,961 | 1268 | 124 | 5 | 2.51 | 2.38 | 0.97–5.83 | 109 | 3 | 1.71 | 1.63 | 0.52–5.13 |
| Venereal warts | 79,502 | 732 | 129 | 1 | 0.84 | 0.77 | 0.11–5.53 | 111 | 1 | 0.98 | 0.89 | 0.12–6.35 |
| Fever | 56,413 | 22,583 | 80 | 49 | 1.53 | 1.53 | 1.06–2.21 | 74 | 37 | 1.25 | 1.23 | 0.82–1.86 |
| Smoking (all) | 59,191 | 21,074 | 94 | 36 | 1.08 | 1.11 | 0.75–1.65 | 78 | 34 | 1.22 | 1.26 | 0.83–1.91 |
| 1–9 cigarettes/day | 69,509 | 10,756 | 118 | 12 | 0.70 | 0.71 | 0.39–1.30 | 101 | 11 | 0.78 | 0.79 | 0.42–1.49 |
| 10 or more cigarettes/day | 69,947 | 10,318 | 106 | 24 | 1.46 | 1.57 | 0.98–2.54 | 89 | 23 | 1.69 | 1.80 | 1.10–2.94 |

*aHR*, adjusted hazard ratio; *CI*, confidence interval; *CP*, cerebral palsy; *HR*, hazard ratio.

[a] All adjusted for maternal age (younger than 35, 35–39, 40–44, 45 years old or older), alcohol drink per week (never, 1 or fewer, 2–4, 5 or more), binge drinking, combined socioeconomic status group (1, 2, 3), season of birth (fall, winter, spring, summer), number per household (1, 2, 3, 4 or more), birth year (before 2000, 2000 or later), and smoking (0, 1–9, ≥10) except in analysis in which smoking is an exposure.

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## TABLE 3

HRs for sCP based on combined exposures to smoking ≥10 cigarettes per day and vaginal infections

| | Smoking 10 cigarettes or more per day | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Unexposed | | | Exposed | | | Total | | |
| Vaginal infections | n | sCP, n | HR (95% CI) | n | sCP, n | HR (95% CI) | n | sCP, n | HR (95% CI) |
| Unexposed | 54,707 | 60 | 1 (reference) | 8034 | 17 | 2.06 (1.17– 3.62) | 62,741 | 77 | 1 (reference) |
| Exposed | | | | | | | | | |
| Untreated | 6641 | 14 | 1.95 (1.08– 3.49) | 953 | 4 | 3.99 (1.45– 11.0) | 7594 | 18 | 1.95 (1.17– 3.26) |
| Treated | 7880 | 15 | 1.78 (1.00– 3.16) | 1229 | 2 | 1.62 (0.40– 6.65) | 9109 | 17 | 1.56 (0.92–2.65) |
| Total | 69,228 | 89 | 1 (reference) | 10,216 | 23 | 1.86 (1.15– 3.03) | | | |

*CI*, confidence interval; *CP*, cerebal palsy; *HR*, hazard ratio; *sCP*, spastic cerebal palsy.

All adjusted for maternal age (younger than 35, 35–39, 40–44, 45 years old or older), alcohol drinks per week (never, ≤1, 2–4, ≥5), binge drinking, combined socioeconomic status group (1, 2, 3), season of birth (fall, winter, spring, summer), number per household (1, 2, 3, ≥4), birth year (before 2000, 2000 or later), and smoking (0, 1–9, ≥10 cigarettes per day) except in analysis in which smoking is an exposure.

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## TABLE 4

Hazard ratios for CP based on combined exposures to maternal fever and vaginal infections

| | Fever | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Unexposed | | | Exposed | | | Total | | |
| Vaginal infections | n | CP, n | HR (95% CI) | n | CP, n | HR (95% CI) | n | CP, n | HR (95% CI) |
| Unexposed | 44,440 | 57 | 1 (reference) | 17,357 | 35 | 1.58 (1.08– 2.30) | 61,797 | 92 | 1 (reference) |
| Exposed | 11,398 | 23 | 1.61 (0.93– 2.79) | 5026 | 14 | 2.22 (1.08– 4.56) | 16,424 | 37 | 1.54 (0.89–2.66) |
| Total | 55,838 | 80 | 1 (reference) | 22,383 | 49 | 1.53 (1.10–2.12) | | | |

*CI*, confidence interval; *CP*, cerebal palsy; *HR*, hazard ratio.

All adjusted for maternal age (younger than 35, 35–39, 40–44, 45 years old or older), alcohol drinks per week (never, ≤1, 2–4, ≥5), binge drinking, combined socioeconomic status group (1, 2, 3), season of birth (fall, winter, spring, summer), number per household (1, 2, 3, ≥4), birth year (before 2000, 2000 or later), and smoking (0, 1–9, ≥10 cigarettes per day) except in analysis in which smoking is an exposure.

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**TABLE 5**

HRs for CP and exposures to vaginal infection, fever, and smoking by Apgar score

| | Apgar <10 | | | | | | | Apgar = 10 | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Number | | | | | | | Number | | | | | | |
| | Non-CP | | CP | | | | | Non-CP | | CP | | | | |
| Factors | Unexposed | Exposed | Unexposed | Exposed | Crude HR | aHR[a] | 95% CI | Unexposed | Exposed | Unexposed | Exposed | Crude HR | aHR[a] | 95% CI |
| Vaginal infections (all) | 4486 | 1236 | 31 | 13 | 1.52 | 1.54 | (0.79–2.99) | 57,693 | 15,298 | 61 | 23 | 1.42 | 1.45 | (0.77–2.71) |
| Untreated | 5181 | 541 | 36 | 8 | 2.13 | 2.11 | (0.97–4.61) | 66,007 | 6984 | 75 | 9 | 1.22 | 1.24 | (0.58–2.67) |
| Treated | 5027 | 695 | 39 | 5 | 1.04 | 1.08 | (0.44–2.61) | 64,677 | 8314 | 70 | 14 | 1.59 | 1.62 | (0.79–3.32) |
| Fever | 4065 | 1635 | 30 | 13 | 1.08 | 1.16 | (0.53–2.50) | 51,873 | 20,761 | 49 | 35 | 1.78 | 1.74 | (1.04–2.91) |
| Smoking (all) | 4257 | 1526 | 37 | 7 | 0.53 | 0.55 | (0.24–1.25) | 54,443 | 19,367 | 56 | 28 | 1.40 | 1.45 | (0.91–2.30) |
| 1–9 cigarettes/d | 4998 | 785 | 42 | 2 | 0.30 | 0.29 | (0.06–1.31) | 63,926 | 9884 | 74 | 10 | 0.98 | 1.01 | (0.41–2.46) |
| ≥10 cigarettes/d | 5041 | 742 | 39 | 5 | 0.78 | 0.87 | (0.35–2.16) | 64,327 | 9483 | 66 | 18 | 1.84 | 1.94 | (1.18–3.17) |

*aHR*, adjusted hazard ratio; *CI*, confidence interval; *CP*, cerebral palsy; *HR*, hazard ratio.

[a]All adjusted for maternal age (younger than 35, 35–39, 40–44, 45 years old or older), alcohol drink per week (never, 1 or fewer, 2–4, 5 or more), binge drinking, combined socioeconomic status group (1, 2, 3), season of birth (fall, winter, spring, summer), number per household (1, 2, 3, 4 or more), birth year (before 2000, 2000 or later), and smoking (0, 1–9, 10) except in analysis in which smoking is an exposure.

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**TABLE 6**

HRs for sCP and exposures to vaginal infection, fever, and smoking by Apgar score

| | Apgar <10 | | | | | | | Apgar = 10 | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Number | | | | | | | Number | | | | | | |
| | Non-CP | | CP | | | | | Non-CP | | CP | | | | |
| Factors | Unexposed | Exposed | Unexposed | Exposed | Crude HR | aHR[a] | 95% CI | Unexposed | Exposed | Unexposed | Exposed | Crude HR | aHR[a] | 95% CI |
| Vaginal infections (all) | 4486 | 1236 | 23 | 13 | 2.05 | 2.07 | (1.03–4.13) | 57,693 | 15,298 | 53 | 21 | 1.49 | 1.51 | (0.81–2.81) |
| Untreated | 5181 | 541 | 28 | 8 | 2.87 | 2.80 | (1.23–6.33) | 66,007 | 6984 | 65 | 9 | 1.4 | 1.42 | (0.67–3.04) |
| Treated | 5027 | 695 | 31 | 5 | 1.40 | 1.46 | (0.59–3.59) | 64,677 | 8314 | 62 | 12 | 1.57 | 1.59 | (0.77–3.28) |
| Fever | 4065 | 1635 | 26 | 9 | 0.86 | 0.94 | (0.42–2.09) | 51,873 | 20,761 | 47 | 27 | 1.43 | 1.36 | (0.81–2.27) |
| Smoking (all) | 4257 | 1526 | 30 | 6 | 0.56 | 0.56 | (0.23–1.34) | 54,443 | 19,367 | 47 | 27 | 1.61 | 1.68 | (0.99–2.86) |
| 1–9 cigarettes/day | 4998 | 785 | 35 | 1 | 0.18 | 0.18 | (0.02–1.36) | 63,926 | 9884 | 64 | 10 | 1.17 | 1.22 | (0.47–3.16) |
| ≥10 cigarettes/day | 5041 | 742 | 31 | 5 | 0.96 | 1.03 | (0.40–2.61) | 64,327 | 9483 | 57 | 17 | 2.21 | 2.21 | (1.33–3.67) |

*aHR*, adjusted hazard ratio; *CI*, confidence interval; *CP*, cerebral palsy; *HR*, hazard ratio.

[a]All adjusted for maternal age (younger than 35, 35–39, 40–44, 45 years old or older), alcohol drink per week (never, 1 or fewer, 2–4, 5 or more), binge drinking, combined socioeconomic status group (1, 2, 3), season of birth (fall, winter, spring, summer), number per household (1, 2, 3, 4 or more), birth year (before 2000, 2000 or later), and smoking (0, 1–9, 10) except in analysis in which smoking is an exposure.

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## TABLE 7

Sensitivity analyses using complete case analysis and eliminating postpartum interviews compared with main analyses results

| | All CP outcomes | | | | sCP outcomes | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Vaginal infections | | Fever | | Vaginal infections | | Untreated vaginal infections | | Smoking >10cigarettes/d | |
| Variable | aHR[a] | 95% CI | aHR | 95% CI | aHR | 95% CI | aHR | 95% CI | aHR | 95% CI |
| Main analysis | 1.52 | (1.04–2.24) | 1.53 | (1.06–2.21) | 1.73 | (1.16–2.60) | 1.95 | (1.16–3.26) | 1.8 | (1.10–2.94) |
| Complete case analysis | 1.5 | (0.88–2.53) | 1.52 | (1.09–2.12) | 1.71 | (1.01–2.88) | 1.86 | (1.01–3.45) | 1.89 | (1.23–2.91) |
| Postpartum interviews eliminated | 1.52 | (0.89–2.61) | 1.53 | (1.10–2.12) | 1.73 | (1.01– 2.97) | 1.95 | (1.04–3.65) | 1.8 | (1.17–2.75) |

*aHR*, adjusted hazard ratio; *CI*, confidence interval; *CP*, cerebal palsy; *sCP*, spastic cerebal palsy.

[a] All adjusted for maternal age (younger than 35, 35–39, 40–44, 45 years old or older), alcohol drinks per week (never, 1, 2–4, 5), binge drinking, combined socioeconomic status group (1, 2, 3), season of birth (fall, winter, spring, summer), number per household (1, 2, 3, 4), birth year (before 2000, 2000 or later), and smoking (0, 1–9, 10 cigarettes per day) except in analysis in which smoking is an exposure.

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