BACKGROUND: Evidence indicates that in utero exposure to chorioamnionitis might increase the risk of neurodevelopmental disorders in the offspring. However, findings on this topic have been inconsistent.

OBJECTIVE: To examine the association between chorioamnionitis and neurodevelopmental disorders in offspring.

STUDY DESIGN: This was a retrospective population-based cohort study in Sweden. A total of 2,228,280 singleton live births and stillbirths between 1998 and 2019 were included in our study population. Data on maternal characteristics and neurodevelopmental disorders in offspring were obtained by individual record-linkages of nationwide Swedish registries. Chorioamnionitis was identified using the National Medical Birth Register. Inpatient and outpatient diagnoses were obtained for cerebral palsy, autism, attention deficit hyperactivity disorder, epilepsy, and intellectual disability. Multivariable Cox proportional hazards regression was used to estimate the association between chorioamnionitis and each neurodevelopmental disorder with adjusted hazard ratios and 95% confidence intervals. A causal mediation analysis of the relationship between chorioamnionitis and neurodevelopmental disorders with preterm delivery was performed.

RESULTS: A total of 5770 (0.26%) offspring were exposed to chorioamnionitis during pregnancy. During the study’s follow-up time there were 4752 (0.21%) cases of cerebral palsy, 17,897 (0.80%) cases of autism, 14,574 (0.65%) cases of attention deficit hyperactivity disorder, and 14,574 (0.65%) cases of intellectual disability. After adjusting for potential confounders, exposure to chorioamnionitis increased the hazard ratios of cerebral palsy (adjusted hazard ratio, 7.43; 95% confidence interval, 5.90–9.37), autism (adjusted hazard ratio, 1.43; 95% confidence interval, 1.21–1.68), attention deficit hyperactivity disorder (adjusted hazard ratio, 1.17; 95% confidence interval, 1.03–1.33), and intellectual disability (adjusted hazard ratio, 1.99; 95% confidence interval, 1.53–2.58), whereas chorioamnionitis was not significantly associated with higher rates of epilepsy in offspring. Mediation analysis revealed that these associations were mainly explained through preterm delivery; however, increased risk was also observed among term infants.

CONCLUSION: Chorioamnionitis increases the risk of neurodevelopmental disorders, particularly cerebral palsy, autism, attention deficit hyperactivity disorder, and intellectual disability. These associations were mainly mediated through preterm delivery. Efforts for timely identification and appropriate interventions to treat infections during pregnancy will have sustained benefits in reducing the burden of neurologic complications in children at the population level.

Key words: attention deficit hyperactivity disorder, autism, cerebral palsy, chorioamnionitis, epilepsy, intellectual disability, intraamniotic inflammation, intraamniotic infection, neurodevelopmental disorders

Introduction
Neurodevelopmental disorders represent a significant public health issue worldwide and are responsible for a considerable proportion of the global burden of disease. Over the last decades, there has been a rise in the prevalence of neurodevelopmental disorders and an increase in the number of individuals acquiring such diagnosis. Many risk factors are likely to operate during fetal life and infancy, the earliest and most sensitive stages of brain development.

Evidence indicates that maternal infections, in particular chorioamnionitis, might negatively affect the sensitive fetal brain and lead to brain injury, adverse neurodevelopmental outcomes, and an increased lifetime risk of specific psychiatric diseases. Clinical chorioamnionitis is globally the most common infection-related complication in labor and delivery wards and is estimated to have a prevalence of 1% to 6% in all pregnancies in the United States, whereas intraamniotic infection might be present in 10% of patients with perterm labor. Clinical chorioamnionitis has been characterized as a syndrome rather than a single entity, linked with proven intraamniotic infection, sterile intraamniotic inflammation, or signs of a maternal systemic inflammatory process without intraamniotic inflammation. The diagnostic criteria involve the presence of fever with 2 or more of the following: maternal or fetal tachycardia, maternal leukocytosis, tenderness of the uterus, and purulent or malodorous amniotic fluid.

Chorioamnionitis has been shown to be associated with long-term neonatal outcomes, such as cerebral palsy. However, epidemiologic evidence about the association between chorioamnionitis and risks of other long-term neurologic disorders in offspring is limited. Therefore, in this Swedish nationwide population-based cohort study of >2 million singleton births, we...
Evidence indicates that in utero exposure to chorioamnionitis might increase the risk of neurodevelopmental outcomes in the offspring. However, findings on this topic have been inconsistent. This study aimed to examine the association between chorioamnionitis and long-term neurodevelopmental disorders in the offspring.

Key findings
Chorioamnionitis increases the risk of neurodevelopmental disorders, particularly cerebral palsy, autism, attention deficit hyperactivity disorder (ADHD), and intellectual disability. These associations were mediated through preterm birth; however, increased risk was also observed among term infants.

What does this add to what is known?
Chorioamnionitis was associated with increased hazard ratios of 7.43 for cerebral palsy, 1.43 for autism, 1.17 for ADHD, and 1.99 for intellectual disability in the offspring (compared with offspring not exposed to chorioamnionitis), even after adjusting for several potential confounders. Preterm delivery accounted for a large proportion of the neurodevelopmental disorder risk associated with chorioamnionitis.

Aim
To investigate the association between chorioamnionitis and long-term neurodevelopmental disorders in offspring, in particular cerebral palsy, autism, attention deficit hyperactivity disorder (ADHD), epilepsy, and intellectual disability. We also examined the extent to which preterm delivery mediates the effect of chorioamnionitis on neurodevelopmental disorders in offspring. We hypothesized that the exposure to chorioamnionitis is associated with increased risks of long-term neurodevelopmental disorders in offspring.

Materials and Methods
Using the Swedish Medical Birth Register, our cohort comprised all singleton births at ≥22 completed gestational weeks in Sweden from January 1, 1998, through December 31, 2019. Using the unique personal national registration numbers of mothers and their offspring the Medical Birth Register was cross-linked with the nation-wide National Patient, National Prescribed Drug, Total Population and Education Registers. Since 1997, diseases have been coded according to the Swedish version of the International Classification of Diseases, Tenth Revision (ICD-10). The Anatomical Therapeutic Chemical Classification System and the Drug Identification Numbers were used to retrieve the prescription medications for ADHD.

Exposure
Women with chorioamnionitis were identified from the Medical Birth Register with diagnosis records for the ICD-10 code O41.1 (including diagnoses of infection of amniotic sac and membranes, chorioamnionitis, and amnionitis) and their infants’ records including the ICD-10 code P02.7 (fetus or newborn affected by complications of placenta, cord, and membranes: chorioamnionitis). This case definition refers to clinical chorioamnionitis in the assessment of the clinician treating the mother and/or infant. Results of pathologic placental investigations were not available in our data sources.

Disorders
Adverse neurodevelopmental disorders included all clinically ascertained diagnoses of cerebral palsy, epilepsy, autism, ADHD, and intellectual disability. Children with epilepsy who had also cerebral palsy were not included in the epilepsy group. Diagnoses were identified from birth until December 31, 2020, in the National Patient Register and the prescription registry using ICD-10 codes (Supplemental Table 1 shows specific codes). In Sweden, all infants and preschool children regularly undergo routine medical and developmental examinations. At 4 years of age, a mandatory assessment of motor, language, cognitive, and social development is conducted. Children who are suspected of having a developmental disorder are referred to a specialist team for further assessment, with any diagnostic information reported to the National Patient Register.

Covariates
We obtained maternal information about the country of birth, age at child’s birth, early-pregnancy body mass index (BMI), height, parity, years of education, smoking during pregnancy, cohabitation with a partner, history of psychiatric disorders, prepregnancy hypertension, and diabetes mellitus. Infant’s information included the calendar year of birth, sex, gestational age at birth, birthweight for gestational age, and major congenital malformation. The percentiles of birthweight for gestational age were based on the Swedish fetal growth reference obtained from the Medical Birth Register.

Maternal BMI (kg/m²) was classified according to the World Health Organization as underweight (BMI <18.5), normal weight (18.5–24.9), overweight (25.0–29.9), obesity class I (30.0–34.9), and obesity class II and III (≥35.0). Mothers who reported daily smoking at the first antenatal visit and/or at 30 to 32 gestational weeks were classified as smokers.

The mode of delivery was obtained from obstetrical records and categorized as vaginal noninstrumental, vaginal instrumental, elective cesarean delivery, and emergency cesarean delivery.

Statistical analysis
Baseline demographic characteristics of children born to mothers with and without chorioamnionitis were compared as presented in Table 1.
| Maternal characteristics                  | Total (n=2,228,280) | No chorioamnionitis (N=2,222,510) | Chorioamnionitis (N=5,770) | Pvalue |
|------------------------------------------|---------------------|-----------------------------------|---------------------------|--------|
| Maternal age (y)                         |                     |                                   |                           |        |
| <19                                      | 32,245 (1.45)       | 32,139 (99.67)                   | 106 (0.33)                | <.001  |
| 20—24                                    | 278,510 (12.50)     | 277,805 (99.75)                  | 705 (0.25)                |        |
| 25—29                                    | 689,567 (30.95)     | 687,805 (99.74)                  | 1762 (0.26)               |        |
| 30—34                                    | 768,023 (34.47)     | 766,201 (99.76)                  | 1822 (0.24)               |        |
| ≥35                                      | 459,935 (20.64)     | 458,560 (99.70)                  | 1375 (0.30)               |        |
| Country of birth                         |                     |                                   |                           | <.001  |
| Nordic                                   | 1,747,142 (78.41)   | 1,742,965 (99.76)                | 4177 (0.24)               |        |
| Non-Nordic                               | 478,948 (21.49)     | 477,364 (99.67)                  | 1584 (0.33)               |        |
| Data missing                             | 2190 (0.10)         | 2181 (99.59)                     | 9 (0.41)                  |        |
| Education (y)                            |                     |                                   |                           | <.001  |
| ≤9                                       | 189,100 (8.49)      | 188,507 (99.69)                  | 593 (0.31)                |        |
| 10—11                                    | 258,711 (11.61)     | 257,923 (99.70)                  | 788 (0.30)                |        |
| 12                                       | 570,843 (25.62)     | 569,403 (99.75)                  | 1440 (0.25)               |        |
| 13—14                                    | 320,862 (14.40)     | 319,996 (99.73)                  | 866 (0.27)                |        |
| ≥15                                      | 867,879 (38.95)     | 865,870 (99.77)                  | 2009 (0.23)               |        |
| Data missing                             | 20,885 (0.94)       | 20,811 (99.65)                   | 74 (0.35)                 |        |
| Mother cohabits with partner             |                     |                                   |                           | <.001  |
| Yes                                      | 1,986,484 (89.15)   | 1,981,738 (99.76)                | 4746 (0.24)               |        |
| No                                       | 128,252 (5.76)      | 127,729 (99.79)                  | 523 (0.41)                |        |
| Data missing                             | 113,544 (5.10)      | 113,043 (99.56)                  | 501 (0.44)                |        |
| Parity                                   |                     |                                   |                           | <.001  |
| 1                                        | 977,410 (43.86)     | 973,492 (99.60)                  | 3918 (0.40)               |        |
| 2                                        | 823,667 (36.96)     | 822,527 (99.86)                  | 1140 (0.14)               |        |
| 3                                        | 298,019 (13.37)     | 297,579 (99.85)                  | 440 (0.15)                |        |
| ≥4                                       | 129,184 (5.80)      | 128,912 (99.79)                  | 272 (0.21)                |        |
| Maternal height (cm)                     |                     |                                   |                           | <.001  |
| ≤159                                     | 307,412 (13.80)     | 306,308 (99.64)                  | 1104 (0.36)               |        |
| 160—164                                  | 565,833 (25.39)     | 564,220 (99.71)                  | 1613 (0.29)               |        |
| 165—169                                  | 635,203 (28.51)     | 633,651 (99.76)                  | 1552 (0.24)               |        |
| ≥170                                     | 686,815 (30.82)     | 685,488 (99.81)                  | 1327 (0.19)               |        |
| Data missing                             | 33,017 (1.48)       | 32,843 (99.47)                   | 174 (0.53)                |        |
| Smoking                                  |                     |                                   |                           | <.001  |
| No                                       | 1,970,016 (88.41)   | 1,965,174 (99.75)                | 4842 (0.25)               |        |
| Yes                                      | 169,202 (7.59)      | 168,704 (99.71)                  | 498 (0.29)                |        |
| Data missing                             | 89,062 (4.00)       | 88,632 (99.52)                   | 430 (0.48)                |        |

Tsamantioti. Chorioamnionitis and the risk of long-term neurodevelopmental disorders in offspring. Am J Obstet Gynecol 2022. (continued)
| Maternal characteristics                        | Total (n=2,228,280) | No chorioamnionitis (N=2,222,510) | Chorioamnionitis (N=5,770) | P-value |
|------------------------------------------------|---------------------|-----------------------------------|---------------------------|---------|
| **Year of delivery**                            |                     |                                   |                           |         |
| 1998—1999                                      | 164,677 (7.39)      | 164,345 (99.80)                   | 332 (0.20)                | <.001   |
| 2000—2004                                      | 453,815 (20.37)     | 452,897 (99.80)                   | 918 (0.20)                |         |
| 2005—2008                                      | 402,523 (18.06)     | 401,727 (99.80)                   | 796 (0.20)                |         |
| 2009—2012                                      | 430,092 (19.30)     | 429,119 (99.77)                   | 973 (0.23)                |         |
| 2013—2015                                      | 329,119 (14.77)     | 328,094 (99.69)                   | 1025 (0.31)               |         |
| 2016—2019                                      | 448,054 (20.11)     | 446,328 (99.61)                   | 1726 (0.39)               |         |
| **Maternal body mass index**                    |                     |                                   |                           |         |
| <18.5                                          | 50,502 (2.27)       | 50,409 (99.82)                    | 93 (0.18)                 | <.001   |
| 18.5—24.9                                      | 1,224,691 (54.96)   | 1,222,204 (99.80)                 | 2487 (0.20)               |         |
| 25.0—29.9                                      | 514,705 (23.10)     | 513,222 (99.71)                   | 1483 (0.29)               |         |
| 30.0—34.9                                      | 177,365 (7.96)      | 176,693 (99.62)                   | 672 (0.38)                |         |
| ≥35.0                                          | 74,939 (3.36)       | 74,557 (99.49)                    | 382 (0.51)                |         |
| Missing                                        | 186,078 (8.35)      | 185,425 (99.65)                   | 653 (0.35)                |         |
| **Pregestational diabetes mellitus**            |                     |                                   |                           |         |
| No                                             | 2,188,462 (98.21)   | 2,182,864 (99.74)                 | 5598 (0.26)               | <.001   |
| Yes                                            | 39,818 (1.79)       | 39,646 (99.57)                    | 172 (0.43)                |         |
| **Pregestational hypertension**                 |                     |                                   |                           | .431    |
| No                                             | 2,213,181 (99.32)   | 2,207,455 (99.74)                 | 5726 (0.26)               |         |
| Yes                                            | 15,099 (0.68)       | 15,055 (99.71)                    | 44 (0.29)                 |         |
| **Any psychiatric diagnoses**                   |                     |                                   |                           | <.001   |
| No                                             | 1,987,049 (89.17)   | 1,982,158 (99.75)                 | 4891 (0.25)               |         |
| Yes                                            | 241,231 (10.83)     | 240,352 (99.64)                   | 879 (0.36)                |         |
| **Mode of delivery**                           |                     |                                   |                           |         |
| Vaginal noninstrumental                        | 1,704,444 (76.49)   | 1,702,571 (99.89)                 | 1873 (0.11)               | <.001   |
| Vaginal instrumental                           | 153,563 (6.89)      | 153,123 (99.71)                   | 440 (0.29)                |         |
| Elective cesarean delivery                     | 182,067 (8.17)      | 181,859 (99.89)                   | 208 (0.11)                |         |
| Emergency cesarean delivery                    | 173,621 (7.79)      | 170,426 (98.16)                   | 3195 (1.84)               |         |
| Data missing                                   | 14,585 (0.65)       | 14,531 (99.63)                    | 54 (0.37)                 |         |
| **Gestational age at delivery (wk)**            |                     |                                   |                           | <.001   |
| ≥37                                            | 2,116,876 (95.00)   | 2,113,213 (99.83)                 | 3663 (0.17)               |         |
| 32—36                                          | 93,085 (4.18)       | 92,326 (99.18)                    | 759 (0.82)                |         |
| 28—31                                          | 10,770 (0.48)       | 10,278 (95.43)                    | 492 (4.57)                |         |
| 22—27                                          | 6408 (0.29)         | 5563 (86.81)                      | 845 (13.19)               |         |
| Data missing                                   | 1141 (0.05)         | 1130 (99.04)                      | 11 (0.96)                 |         |
| **Newborn’s sex**                              |                     |                                   |                           | <.001   |
| Male                                           | 1,146,581 (51.46)   | 1,143,493 (99.73)                 | 3088 (0.27)               |         |
| Female                                         | 1,081,685 (48.54)   | 1,079,003 (99.75)                 | 2682 (0.25)               |         |
| Data missing                                   | 14 (0.00)           | 14 (100)                          | 0 (0.00)                  |         |

Tsamantioti. Chorioamnionitis and the risk of long-term neurodevelopmental disorders in offspring. Am J Obstet Gynecol 2022. (continued)
Summaries of categorical variables were presented in absolute numbers and proportions (%), whereas statistical significance was assessed by the Pearson chi-square test. Cumulative hazard curves were used to compare risks of each neurodevelopmental outcome over time according to chorioamnionitis status. The differences between the curves were assessed using the log-rank test. We calculated hazard ratios (HRs) and the corresponding 2-sided Wald-type 95% confidence intervals (CIs) using Cox proportional hazards regression models, which allowed detailed adjustment for censoring depending on the length of follow-up of each child. Each child was followed up from birth until the diagnosis of the outcome, death, emigration, or end of follow-up on December 31, 2020, whichever occurred first.

Adjusted HRs were obtained from multivariable Cox models in 3 steps, gradually adjusting for additional potential confounders. In model 1, we adjusted for maternal age at child’s birth, parity, maternal educational level, country of mother’s birth, smoking during pregnancy, maternal height, early-pregnancy BMI, any psychiatric disorders, child’s sex, calendar year of birth, and cohabitation with a partner. In model 2, we also adjusted for major congenital malformations, and in model 3, additional adjustment was made for the mode of delivery. The robust sandwich estimate of the covariance matrix was used to calculate 95% CIs in all Cox models to account for the sequential births to the same mother.

Causal mediation analysis
We considered preterm birth (<37 weeks) as a potential mediator for the effect of chorioamnionitis on cerebral palsy, autism, ADHD, and intellectual disability (Supplemental Figure, Supplemental Table 2, Supplemental Table 3). Therefore, we undertook causal mediation analyses based on a counterfactual framework to disentangle the association between chorioamnionitis and the outcomes (ie, total effect) into the natural direct effect (the association between chorioamnionitis and the outcomes [cerebral palsy, autism, ADHD, and intellectual disability] in the absence of preterm birth) and the natural indirect effect (the association operating through the mediators). We also estimated the controlled direct effect, which provided an estimate of the effect of chorioamnionitis on the outcomes that is not mediated through preterm birth (ie, among term births). We also assessed the proportion of the total effect (on the HR scale) between chorioamnionitis and the outcome(s) that was mediated through preterm delivery. Furthermore, we created a composite mediator of preterm delivery and neonatal infection, and preterm delivery and respiratory distress syndrome (RDS), diagnosed at 0 to 27 days of age, to examine the joint mediation effect of neonatal morbidity and preterm delivery on the association between chorioamnionitis and the disorders.

Sensitivity analyses
We performed several sensitivity analyses. First, because mediation methods were developed under a strict no-unmeasured-confounding assumption, we examined the robustness of causal effects to unmeasured confounders by estimating an E-value (defined as the maximal strength of association that an unmeasured confounder would need to have with the exposure and the outcome to fully explain away an observed exposure–outcome association). Second, given that death before the diagnosis of outcome would preclude a child
from being diagnosed with such conditions in the future, we also quantified the adjusted association between chorioamnionitis and a composite outcome including any of the following: stillbirth, infant mortality (ie, death within the first year after birth), or any neurodevelopmental disorder (ie, stillbirth, infant death, or epilepsy). Logistic regression analyses were used to assess the association between chorioamnionitis and each composite outcome, adjusting for the same founders noted in model 2.

Third, to focus only on potentially clinically relevant cases of neurodevelopmental disorders, we restricted the age at diagnosis: 3+ years of age for ADHD and intellectual disability, 1+ years of age for diagnoses of autism, and 26+ days of age for epilepsy. Fourth, to address missing values of covariates in our cohort and the possible bias that it could introduce, we performed multiple imputation with chained equations under the assumption of missing at random. All analyses were performed using Stata statistical software, version 16 (StataCorp, College Station, TX) and SAS, version 9.4 (SAS Institute, Cary, NC).

Results
Between January 1, 1998 and December 31, 2019, the Medical Birth Register recorded information of about 2,228,290 singleton live births and stillbirths with valid national registration numbers for mothers and children. After excluding 10 births with missing information on child’s sex and maternal age, the final study cohort included 2,228,280 singleton births.

Demographic and clinical characteristics
Overall, there were 5570 (0.26%) offspring of mothers with chorioamnionitis. During the study follow-up, cerebral palsy was diagnosed in 4752 (0.21%), epilepsy in 17,897 (0.80%), autism in 50,570 (2.27%), ADHD in 114,087 (5.12%), and intellectual disability in 14,574 (0.65%) children. The median age at diagnosis of cerebral palsy was 2.04 years (interquartile range [IQR], 1.10–3.95), 5.60 years (IQR, 2.20–9.82) for epilepsy, 10.49 years (IQR, 6.29–14.14) for autism, 11.04 years (IQR, 6.54–14.31) for ADHD, and 8.86 years (IQR, 5.23–12.56) for intellectual disability. Compared with women without chorioamnionitis, those with chorioamnionitis were more likely to be older (≥35 years), non-Nordic, to live without a partner, to smoke, to be obese (BMI >30.0), to be nulliparous, and to have a lower education. Women with chorioamnionitis were more likely to have a history of psychiatric disorders (Table 1). Furthermore, women with chorioamnionitis had elevated rates of emergency cesarean delivery, preterm birth, premature rupture of membranes, and small-for-gestational age (SGA <10th percentile) infants.
| Offspring outcome                      | Number of cases | Child-years | Rate $^b$ | Hazard ratio (95% CI)       |
|---------------------------------------|-----------------|-------------|-----------|----------------------------|
|                                       |                 |             |           | Crude  | Model 1 $^b$ | Model 2 $^c$ | Model 3 $^d$|
| Cerebral palsy                        |                 |             |           |        |             |             |             |
| With chorioamnionitis                 | 93              | 46,743      | 19.89     | 9.05 (7.37—11.11) | 7.43 (5.90—9.37) | 6.61 (5.24—8.34) | 4.48 (3.53—5.70) |
| Without chorioamnionitis              | 4659            | 23,028,205  | 2.02      | Ref.   | Ref.        | Ref.        | Ref.        |
| Epilepsy                              |                 |             |           |        |             |             |             |
| With chorioamnionitis                 | 37              | 46,886      | 7.89      | 1.00 (0.73—1.39) | 0.98 (0.70—1.38) | 0.93 (0.66—1.31) | 0.88 (0.62—1.24) |
| Without chorioamnionitis              | 17,860          | 22,926,563  | 7.79      | Ref.   | Ref.        | Ref.        | Ref.        |
| Autism                                |                 |             |           |        |             |             |             |
| With chorioamnionitis                 | 185             | 46,855      | 39.48     | 1.90 (1.65—2.20) | 1.43 (1.21—1.68) | 1.40 (1.19—1.65) | 1.32 (1.12—1.56) |
| Without chorioamnionitis              | 50,385          | 22,868,756  | 22.03     | Ref.   | Ref.        | Ref.        | Ref.        |
| Attention deficit hyperactivity disorder |               |             |           |        |             |             |             |
| With chorioamnionitis                 | 305             | 46,224      | 65.98     | 1.43 (1.28—1.60) | 1.17 (1.03—1.33) | 1.16 (1.02—1.32) | 1.11 (0.98—1.26) |
| Without chorioamnionitis              | 113,782         | 22,623,194  | 50.29     | Ref.   | Ref.        | Ref.        | Ref.        |
| Intellectual disability               |                 |             |           |        |             |             |             |
| With chorioamnionitis                 | 77              | 47,072      | 16.35     | 2.75 (2.20—3.45) | 1.99 (1.53—2.58) | 1.78 (1.37—2.32) | 1.60 (1.23—2.08) |
| Without chorioamnionitis              | 14,497          | 22,996,338  | 6.30      | Ref.   | Ref.        | Ref.        | Ref.        |

$^b$ Rate is calculated as number of cases per 10,000 person-years; $^c$ Model 1 adjusted for maternal age at child birth, parity, maternal educational level, country of mother’s birth, smoking during pregnancy, maternal height, early-pregnancy BMI, any psychiatric disorders, child’s sex, calendar year of birth, and cohabitation with a partner; $^d$ Model 2: in addition to the factors noted in model 1, also adjusted for major malformation; $^e$ Model 3: in addition to the factors noted in model 2, also adjusted for mode of delivery.
### TABLE 3
Causal mediation analysis to estimate the impact of preterm delivery (<37 weeks) on the association between maternal chorioamnionitis and adverse neurodevelopmental outcomes in offspring. Live-born singleton offspring in Sweden, 1998 to 2019

| Mediators                               | Adjusted HR (95% CI) | Controlled direct effect among term infants | Natural direct effect | Natural indirect effect | Percentage mediated (%) |
|-----------------------------------------|----------------------|--------------------------------------------|-----------------------|-------------------------|-------------------------|
|                                        |                      | Total effect                                |                       |                         |                         |
| Cerebral palsy                          |                      |                                            |                       |                         |                         |
| Preterm birth                           | 7.47 (5.96–9.36)     | 2.63 (1.56–4.45)                           | 2.91 (2.01–4.21)      | 2.57 (1.93–3.41)        | 70                      |
| Preterm and neonatal infection          | 7.19 (5.73–9.01)     | 4.84 (3.57–6.57)                           | 4.67 (3.46–6.29)      | 1.54 (1.29–1.84)        | 41                      |
| Preterm and respiratory distress syndrome| 7.36 (5.87–9.22)    | 4.04 (2.80–5.83)                           | 3.76 (2.68–5.26)      | 1.96 (1.54–2.49)        | 57                      |
| Autism                                  |                      |                                            |                       |                         |                         |
| Preterm birth                           | 1.49 (1.27–1.75)     | 1.14 (0.91–1.43)                           | 1.18 (0.96–1.46)      | 1.26 (1.12–1.42)        | 63                      |
| Preterm and neonatal infection          | 1.50 (1.28–1.75)     | 1.33 (1.11–1.59)                           | 1.33 (1.11–1.59)      | 1.13 (1.05–1.20)        | 34                      |
| Preterm and respiratory distress syndrome| 1.52 (1.30–1.77)    | 1.26 (1.03–1.52)                           | 1.26 (1.05–1.52)      | 1.20 (1.10–1.32)        | 49                      |
| Attention deficit hyperactivity disorder |                      |                                            |                       |                         |                         |
| Preterm birth                           | 1.19 (1.05–1.35)     | 1.02 (0.86–1.20)                           | 1.04 (0.88–1.21)      | 1.15 (1.06–1.24)        | 81                      |
| Preterm and neonatal infection          | 1.20 (1.06–1.36)     | 1.11 (0.97–1.28)                           | 1.11 (0.97–1.28)      | 1.08 (1.03–1.13)        | 44                      |
| Preterm and respiratory distress syndrome| 1.20 (1.07–1.36)    | 1.05 (0.90–1.21)                           | 1.05 (0.91–1.22)      | 1.14 (1.07–1.22)        | 74                      |
| Intellectual disability                 |                      |                                            |                       |                         |                         |
| Preterm birth                           | 1.96 (1.52–2.53)     | 1.23 (0.80–1.91)                           | 1.29 (0.88–1.88)      | 1.52 (1.20–1.93)        | 70                      |
| Preterm and neonatal infection          | 2.01 (1.56–2.58)     | 1.57 (1.15–2.15)                           | 1.57 (1.15–2.14)      | 1.28 (1.11–1.48)        | 43                      |
| Preterm and respiratory distress syndrome| 2.01 (1.56–2.59)    | 1.45 (1.02–2.05)                           | 1.45 (1.04–2.03)      | 1.39 (1.15–1.67)        | 56                      |

BMI, body mass index; CI, confidence interval; HR, hazard ratio.

* Causal effects were adjusted for confounding effects of maternal age at child birth, parity, maternal educational level, country of mother’s birth, smoking during pregnancy, maternal height, early-pregnancy BMI, any psychiatric disorders, child’s sex, calendar year of birth, and cohabitation with a partner.

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Univariable and multivariable analysis

Unadjusted cumulative hazard curves showed a significantly higher cumulative hazard of cerebral palsy, autism, ADHD, and intellectual disability among offspring born to mothers with chorioamnionitis than among those born to mothers without chorioamnionitis (Figure). After adjusting for potential confounders, compared with offspring of mothers without chorioamnionitis, the adjusted HRs were higher for cerebral palsy, autism, ADHD, and intellectual disability in offspring of mothers with chorioamnionitis (Table 2, Model 1), whereas chorioamnionitis was not significantly associated with epilepsy in offspring. Although slightly attenuated, the same pattern of associations remained after adjusting for major malformations and mode of delivery (Table 2, Model 2 and 3).

We examined the impact of preterm delivery on the association between chorioamnionitis and cerebral palsy, autism, ADHD, and intellectual disability (Table 3). The HRs for the natural direct and natural indirect (mediated) effects of chorioamnionitis on cerebral palsy were 2.91 (95% CI, 2.01–4.21) and 2.57 (95% CI, 1.93–3.41), respectively. This indicates that 70% of the total effect of chorioamnionitis on cerebral palsy was mediated through preterm delivery, and about 30% of the total effect was explained through other undiscovered pathways (other than preterm birth). Furthermore, 41% of the total effect was jointly mediated through preterm delivery and neonatal infections, and 57% jointly mediated through preterm delivery and RDS. Similar mediation effects of preterm delivery, neonatal infection, and RDS were also observed for autism, ADHD, and intellectual disability (Table 3).

Sensitivity analyses

In the sensitivity analyses, the E-value for the HR and the lower 95% CI were greater than the observed estimates (Supplemental Table 4). These results suggest that the casual mediation parameters were robust to unmeasured confounding. Analyses addressing the competing risk of death showed similar associations between chorioamnionitis and each composite outcome of death and/or each neurodevelopmental disorder (Supplemental Table 5). Furthermore, restricting the age at diagnosis of the outcomes did not change our results (Supplemental Table 6). The results were also unchanged in supplemental analyses using multiple imputation for missing data (Supplemental Table 7).

Results in the context of what is known

Consistently with our findings, previous studies have found increased risk of neurologic disorders, specifically cerebral palsy, among offspring exposed to chorioamnionitis. In addition, elevated risks of other adverse neurodevelopmental outcomes, such as autism, epilepsy, ADHD, cognitive impairment, speech delay, and hearing loss, have been reported in children exposed to maternal infection or chorioamnionitis, suggesting that exposure to inflammation in utero could alter brain development and function. In contrast, several studies have concluded that chorioamnionitis poses no independent risk on short-term neurodevelopmental outcomes. However, a direct comparison of our results with those of previous studies is hampered by the absence of a uniform, well-established clinical diagnostic algorithm for chorioamnionitis. Consequently, there is large variation in the diagnosis and definition of clinical chorioamnionitis. Clinical chorioamnionitis is frequently used interchangeably with histologically proven chorioamnionitis without being distinguished among clinicians and researchers, further complicating comparisons between individual studies.

Clinical and research implications

Our results demonstrated that the association between chorioamnionitis and neurodevelopmental disorders is mainly mediated through associated neonatal conditions including preterm birth, RDS, and neonatal infections. However, about 30% of the total effect was explained through other undiscovered pathways, and we also observed increased risks of cerebral palsy, autism, and intellectual disability among term infants. Overall, preterm infants are at greater risk of developing major short- and long-term neurodevelopmental disorders. These risks increase with decreasing gestational age at birth, whereas the inflammatory environment in chorioamnionitis decreases with increasing gestational age. Some studies have previously shown associations between preterm birth and neurodevelopmental conditions, including autism, ADHD, cerebral palsy, and cognitive impairment. Our results provide further evidence that preterm birth, triggered by infection such as chorioamnionitis, increases the risk of neurodevelopmental adversity. Chorioamnionitis is also associated with significant neonatal morbidity, such as neonatal sepsis, intraventricular hemorrhage, and respiratory syndrome, which puts the surviving neonates at higher risk of long-term neurologic adversity.

The underlying mechanism linking chorioamnionitis with neurodevelopmental outcomes may involve the activation and upregulation of infection and inflammatory processes in the mother and the fetus. This activation results in the release of cytokines and chemokines from decidua and fetal membranes, such as interleukin-6, which stimulate the synthesis of prostanoids and metalloproteases that can...
lead to the ripening of the cervix, rupture of the membranes, and spontaneous labor or induction of labor and delivery. In addition, chorioamnionitis can induce a fetal inflammatory response syndrome, resulting in the release of inflammatory products and reactive oxygen species, which can directly damage the sensitive fetal cerebral cells, predominantly the white matter, resulting in cerebral palsy and other neurodevelopmental disorders.

**Strengths and limitations**

Our study has several strengths. First, the population-based study design along with high-quality registry data that are prospectively and independently collected minimized the possibility of information bias in our study. Second, we adjusted for a number of important maternal confounders, including maternal BMI, smoking during pregnancy, and maternal psychiatric history. We used the Swedish version of ICD-10 diagnostic codes to ascertain chorioamnionitis and adverse outcomes in the offspring. Although these specific codes have not been externally validated, previous studies have shown that in the Swedish National Inpatient Register, positive predictive values of diagnostic codes are between 85% and 95%. In Sweden, the diagnosis of chorioamnionitis is routinely made by the obstetrician, which adds to the clinical accuracy of the diagnosis and its ascertainment by the ICD codes. Lastly, we quantified the effects of chorioamnionitis on the composite outcome, including death and neurodevelopmental conditions, and thereby addressed the competing risk of death.

Nonetheless, our study might have some limitations. Our outcome ascertainment was based on inpatient—outpatient clinical data and drug register data. Therefore, it is possible that we included only patients with the most severe cases of the disorders who sought clinical help, whereas milder cases were not captured. However, this misclassification of the outcomes is non-differential, thus possibly resulting in an underestimation of the true associations. Furthermore, although the diagnosis of chorioamnionitis was based on specific clinical criteria, the clinical presentation varies between patients, which can lead to variation in diagnosis between clinicians. The incidence of chorioamnionitis was 0.26% in our study, which is lower than reported previously. This discrepancy can imply that only the most severe cases of chorioamnionitis were included in our cohort, and the clinically silent or subclinical cases were not detected. This potential underascertainment of chorioamnionitis could also lead to an underestimation of the true effects. Furthermore, premature or ill newborns might serve as a stimulus for clinicians to investigate their mothers more actively for an underlying infection than mothers of apparently healthy infants, which makes such newborns more likely to receive a diagnosis of chorioamnionitis. However, in our data, all infants’ records for chorioamnionitis coincided with maternal diagnosis, therefore limiting bias. In addition, in our mediation analyses we have assumed that the causal pathways between preterm birth, preterm birth—neonatal infections, and preterm birth—infec tion—RDS are not sequential. Future studies may consider exploring these pathways through a mediation analysis with sequentially ordered causal mediators. Lastly, we cannot exclude that residual confounders by unmeasured or unknown factors could drive the observed association.

**Conclusion**

This study revealed a significant association between chorioamnionitis and neurodevelopmental disorders. A large driver of this risk was preterm delivery; however, increased risk was also observed among term infants. Efforts for timely identification and appropriate interventions to treat infections during pregnancy will have sustained benefits in reducing the burden of neurologic complications in children at the population level.

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The study was approved by the Regional Ethical Review Board at Karolinska Institutet, Stockholm, Sweden (approval number 2020-01545).

The lead author (E.T.) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Appendix

SUPPLEMENTAL FIGURE
Simplified DAG of the relation between chorioamnionitis and neurodevelopmental disorders with preterm delivery as the mediator

ADHD, attention deficit hyperactivity disorder; CP, cerebral palsy.

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SUPPLEMENTAL TABLE 1
International Classification of Diseases-10 codes for maternal and neonatal diseases

| Diseases                          | ICD-10 codes |
|----------------------------------|--------------|
| Maternal complications           |              |
| Prepregnancy hypertension        | I10-I15, 010 and 011 + checkbox<sup>a</sup> |
| Preeclampsia and eclampsia       | 014 and 015  |
| Prepregnancy diabetes mellitus   | E10-E14, 024.0-024.3 |
| Gestational diabetes mellitus    | 024.4        |
| Psychiatric disorders            | F00-F99      |
| Major malformation<sup>b</sup>   | Q00-Q99 — minor excluded |
| Neurodevelopmental disorders     |              |
| Cerebral palsy                   | G80          |
| Autism                           | F840-F845, F848, F849 |
| Attention deficit hyperactivity disorder | F90, F988 and ATC N06B |
| Intellectual disability          | F70-F79      |
| Epilepsy                         | G40          |
| Neonatal morbidity               |              |
| Neonatal infection               | P35-P39      |
| Respiratory distress syndrome    | P22          |

Diseases were defined using the Swedish version of ICD-10.

ICD-10, International Classification of Diseases, tenth revision.

<sup>a</sup> Essential hypertension is also recorded in a checkbox in the prenatal record at first prenatal visit; <sup>b</sup> Diagnosis of malformations is derived from the Medical Birth Register or the Patient Register (also including outpatient hospital care from 2001) at 0–364 days of life. Minor (excluded) malformations are defined by the Swedish National Board of Health and Welfare (https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/dokument-webb/ovrigt/diagnostik-som-inte-ska-rapporteras-om-fosterskador.pdf).

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**SUPPLEMENTAL TABLE 2**

| Variables                  | Preterm birth | Preterm and RDS | Preterm and neonatal infection |
|----------------------------|---------------|-----------------|-------------------------------|
|                            | Odds ratio (95% CI) | Odds ratio (95% CI) | Odds ratio (95% CI) |
| With chorioamnionitis      | 8.85 (8.29–9.44) | 17.31 (16.00–18.71) | 36.29 (32.79–40.17) |
| Without chorioamnionitis   | Reference      | Reference        | Reference                     |

BMI, body mass index; CI, confidence interval; OR, odds ratio; RDS, respiratory distress syndrome.

*Adjusted for confounding effects of maternal age at child’s birth, parity, maternal educational level, country of mother’s birth, smoking during pregnancy, maternal height, early-pregnancy BMI, any psychiatric disorders, child’s sex, calendar year of birth, and cohabitation with a partner.

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**SUPPLEMENTAL TABLE 3**

| Comparison group | Cerebral palsy | Epilepsy | Autism | ADHD | Intellectual disability |
|------------------|---------------|----------|--------|------|-------------------------|
|                  | Odds ratio (95% CI) | Odds ratio (95% CI) | Odds ratio (95% CI) | Odds ratio (95% CI) | Odds ratio (95% CI) |
| Preterm birth    | 7.18 (6.68–7.71) | 1.44 (1.35–1.53) | 1.33 (1.28–1.39) | 1.22 (1.19–1.26) | 2.43 (2.30–2.57) |
| Preterm birth + RDS | 15.46 (14.18–16.85) | 1.66 (1.48–1.86) | 1.72 (1.60–1.84) | 1.44 (1.36–1.51) | 3.24 (2.95–3.56) |
| Preterm birth + neonatal infections | 22.05 (19.46–24.98) | 2.19 (1.82–2.64) | 2.23 (2.00–2.49) | 1.66 (1.52–1.82) | 5.05 (4.41–5.78) |

ADHD, attention deficit hyperactivity disorder; BMI, body mass index; CI, confidence interval; OR, odds ratio; RDS, respiratory distress syndrome.

*Adjusted for confounding effects of maternal age at child’s birth, parity, maternal educational level, country of mother’s birth, smoking during pregnancy, maternal height, early-pregnancy BMI, any psychiatric disorders, child’s sex, calendar year of birth, and cohabitation with a partner.

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### SUPPLEMENTAL TABLE 4
Robustness to unmeasured confounding (E-values) of the total adjusted hazard ratio expressing the relation between chorioamnionitis and cerebral palsy, autism, attention deficit hyperactivity disorder, and intellectual disability liveborn singleton infants in Sweden, 1998 to 2019

| Mediators                                      | Hazard ratio (95% CI) for outcomes | Total effect | E-value for HR | E-value for lower 95% CI |
|------------------------------------------------|-----------------------------------|--------------|----------------|--------------------------|
| **Cerebral palsy**                             |                                   |              |                |                          |
| Preterm birth                                  | 7.47 (5.96–9.36)                  | 14.42        | 11.4           |                          |
| Preterm and neonatal infection                 | 7.19 (5.73–9.01)                  | 13.86        | 10.94          |                          |
| Preterm and respiratory distress syndrome      | 7.36 (5.87–9.22)                  | 14.2         | 11.22          |                          |
| **Autism**                                     |                                   |              |                |                          |
| Preterm birth                                  | 1.49 (1.27–1.75)                  | 2.34         | 1.86           |                          |
| Preterm and neonatal infection                 | 1.50 (1.28–1.75)                  | 2.37         | 1.88           |                          |
| Preterm and respiratory distress syndrome      | 1.52 (1.30–1.77)                  | 2.41         | 1.92           |                          |
| **Attention deficit hyperactivity disorder**   |                                   |              |                |                          |
| Preterm birth                                  | 1.19 (1.05–1.35)                  | 1.67         | 1.28           |                          |
| Preterm and neonatal infection                 | 1.20 (1.06–1.36)                  | 1.69         | 1.31           |                          |
| Preterm and respiratory distress syndrome      | 1.20 (1.07–1.36)                  | 1.69         | 1.34           |                          |
| **Intellectual disability**                    |                                   |              |                |                          |
| Preterm birth                                  | 1.96 (1.52–2.53)                  | 3.33         | 2.41           |                          |
| Preterm and neonatal infection                 | 2.01 (1.56–2.58)                  | 3.41         | 2.49           |                          |
| Preterm and respiratory distress syndrome      | 2.01 (1.56–2.59)                  | 3.43         | 2.49           |                          |

BMI, body mass index; CI, confidence interval; HR, hazard ratio.

* Causal effects were adjusted for confounding effects of maternal age at child’s birth, parity, maternal educational level, country of mother’s birth, smoking during pregnancy, maternal height, early pregnancy BMI, any psychiatric disorders, child’s sex, calendar year of birth, and cohabitation with a partner.

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| Composite outcome                              | N (%) | Crude OR (95% CI) | Adjusted OR (95% CI) |
|-----------------------------------------------|-------|-------------------|----------------------|
| Cerebral palsy (composite outcome)            |       |                   |                      |
| with chorioamnionitis                         | 262 (4.54) | 8.68 (7.66—9.84) | 6.49 (5.12—8.23)    |
| without chorioamnionitis                      | 12,113 (0.55) | Ref. | Ref.               |
| Epilepsy (composite outcome)                  |       |                   |                      |
| with chorioamnionitis                         | 206 (3.57) | 3.21 (2.80—3.69) | 0.89 (0.63—1.25)    |
| without chorioamnionitis                      | 25,314 (1.14) | Ref. | Ref.               |
| Autism (composite outcome)                    |       |                   |                      |
| with chorioamnionitis                         | 354 (6.14) | 2.45 (2.20—2.73) | 1.35 (1.14—1.59)    |
| without chorioamnionitis                      | 57,839 (2.60) | Ref. | Ref.               |
| Attention deficit hyperactivity disorder       |       |                   |                      |
| with chorioamnionitis                         | 474 (8.21) | 1.55 (1.41—1.70) | 1.11 (0.97—1.28)    |
| without chorioamnionitis                      | 121,236 (5.45) | Ref. | Ref.               |
| Intellectual disability (composite outcome)   |       |                   |                      |
| with chorioamnionitis                         | 246 (4.26) | 4.46 (3.93—5.08) | 1.71 (1.31—2.25)    |
| without chorioamnionitis                      | 21,951 (0.99) | Ref. | Ref.               |

BMI, body mass index; CI, confidence interval; OR, odds ratio; Ref., reference.

*a* Model 1 adjusted for maternal age at child’s birth, parity, maternal educational level, country of mother’s birth, smoking during pregnancy, maternal height, early-pregnancy BMI, any psychiatric disorders, child’s sex, cohabitation with a partner, calendar year of birth, and major malformation.

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### SUPPLEMENTAL TABLE 6
Risk of adverse outcomes in offspring born to mothers with chorioamnionitis vs offspring born to mothers without chorioamnionitis after restricting the age at diagnosis. Live-born singleton children in Sweden, 1998 to 2019

| Offspring outcome                  | Number of cases | Child-years | Rate<sup>a</sup> | Hazard ratio (95% CI) | Crude | Model 1<sup>b</sup> | Model 2<sup>c</sup> |
|-----------------------------------|-----------------|-------------|-------------------|-----------------------|-------|---------------------|---------------------|
|                                   |                 |             |                   |                       |       |                     |                     |
| Cerebral palsy                    |                 |             |                   |                       |       |                     |                     |
| with chorioamnionitis            | 93              | 46,716      | 19.91             | 9.06 (7.38—11.13)     | 7.43  | 5.90—9.37           | 6.61 (5.24—8.35)    |
| without chorioamnionitis         | 4644            | 23,011,320  | 2.01              | Ref.                  | Ref.  | Ref.                | Ref.                |
| Epilepsy                          |                 |             |                   |                       |       |                     |                     |
| with chorioamnionitis            | 37              | 46,859      | 7.89              | 1.01 (0.73—1.40)      | 0.99  | 0.70—1.39           | 0.94 (0.68—1.32)    |
| without chorioamnionitis         | 17,683          | 22,910,877  | 7.71              | Ref.                  | Ref.  | Ref.                | Ref.                |
| Autism                            |                 |             |                   |                       |       |                     |                     |
| with chorioamnionitis            | 185             | 46,827      | 39.51             | 1.91 (1.65—2.21)      | 1.43  | 1.22—1.69           | 1.41 (1.20—1.66)    |
| without chorioamnionitis         | 50,238          | 22,851,031  | 21.99             | Ref.                  | Ref.  | Ref.                | Ref.                |
| Attention deficit hyperactivity disorder |     |             |                   |                       |       |                     |                     |
| with chorioamnionitis            | 293             | 46,302      | 63.28             | 1.38 (1.23—1.55)      | 1.12  | 0.99—1.28           | 1.12 (0.98—1.27)    |
| without chorioamnionitis         | 113,245         | 22,606,719  | 50.09             | Ref.                  | Ref.  | Ref.                | Ref.                |
| Intellectual disability           |                 |             |                   |                       |       |                     |                     |
| with chorioamnionitis            | 76              | 47,049      | 16.15             | 2.77 (2.21—3.48)      | 1.98  | 1.52—2.57           | 1.77 (1.36—2.32)    |
| without chorioamnionitis         | 14,275          | 22,981,643  | 6.21              | Ref.                  | Ref.  | Ref.                | Ref.                |

BMI, body mass index; CI, confidence interval; Ref., reference.

<sup>a</sup> Rate is calculated as number of cases per 10,000 person-years; <sup>b</sup> Model 1 adjusted for maternal age at child’s birth, parity, maternal education level, country of mother’s birth, smoking during pregnancy, maternal height, early-pregnancy BMI, any psychiatric disorders, child’s sex, calendar year of birth, and cohabitation with a partner; <sup>c</sup> Model 2: in addition to the factors noted in model 1, also adjusted for major malformation; <sup>d</sup> Diagnoses restricted up to the fifth year of age; <sup>e</sup> Follow-up time starts at twenty-seventh days of age; <sup>f</sup> Follow-up time starts at the first year of life; <sup>g</sup> Follow-up time starts at the third year of age.

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SUPPLEMENTAL TABLE 7
Risk of adverse outcomes in offspring born to mothers with chorioamnionitis vs offspring born to mothers without chorioamnionitis after multiple imputation with chained equations of missing covariates. Live-born singleton children in Sweden, 1998 to 2019

| Offspring outcome               | Number of cases | Child-years | Rate<sup>a</sup> | Hazard ratio (95% CI)                      | Crude  | Model 1<sup>b</sup> | Model 2<sup>c</sup> | Model 3<sup>d</sup> |
|--------------------------------|-----------------|-------------|-------------------|-------------------------------------------|--------|---------------------|---------------------|---------------------|
| Cerebral palsy                 |                 |             |                   |                                           |        |                     |                     |                     |
| With chorioamnionitis          | 93              | 46,743      | 19.89             | 9.05 (7.37—11.11)                         | 7.78 (6.32—9.58) | 6.64 (5.38—8.18) | 4.48 (3.61—5.55)   |
| Without chorioamnionitis       | 4659            | 23,028,205  | 2.02              | Ref.                                      | Ref.   | Ref.                | Ref.                | Ref.                |
| Epilepsy                       |                 |             |                   |                                           |        |                     |                     |                     |
| With chorioamnionitis          | 37              | 46,886      | 7.89              | 1.00 (0.73—1.39)                          | 0.93 (0.67—1.29) | 0.88 (0.63—1.21) | 0.82 (0.59—1.14)   |
| Without chorioamnionitis       | 17,860          | 22,926,563  | 7.79              | Ref.                                      | Ref.   | Ref.                | Ref.                | Ref.                |
| Autism                         |                 |             |                   |                                           |        |                     |                     |                     |
| With chorioamnionitis          | 185             | 46,855      | 39.48             | 1.90 (1.65—2.20)                          | 1.54 (1.33—1.78) | 1.51 (1.30—1.74) | 1.43 (1.23—1.65)   |
| Without chorioamnionitis       | 50,385          | 22,868,756  | 22.03             | Ref.                                      | Ref.   | Ref.                | Ref.                | Ref.                |
| Attention deficit hyperactivity disorder |           |             |                   |                                           |        |                     |                     |                     |
| With chorioamnionitis          | 305             | 46,224      | 65.98             | 1.43 (1.28—1.60)                          | 1.26 (1.12—1.41) | 1.25 (1.11—1.40) | 1.18 (1.06—1.33)   |
| Without chorioamnionitis       | 113,782         | 22,623,194  | 50.29             | Ref.                                      | Ref.   | Ref.                | Ref.                | Ref.                |
| Intellectual disability        |                 |             |                   |                                           |        |                     |                     |                     |
| With chorioamnionitis          | 77              | 47,072      | 16.35             | 2.75 (2.20—3.44)                          | 2.27 (1.81—2.84) | 1.96 (1.56—2.47) | 1.75 (1.39—2.21)   |
| Without chorioamnionitis       | 14,497          | 22,996,338  | 6.30              | Ref.                                      | Ref.   | Ref.                | Ref.                | Ref.                |

BMI, body mass index; CI, confidence interval; Ref., reference.

<sup>a</sup> Rate is calculated as number of cases per 10,000 person-years; <sup>b</sup> Model 1 adjusted for maternal age at child birth, parity, maternal educational level, country of mother’s birth, smoking during pregnancy, maternal height, early-pregnancy BMI, any psychiatric disorders, child’s sex, calendar year of birth, and cohabitation with a partner; <sup>c</sup> Model 2: in addition to the factors noted in model 1, also adjusted for major malformation; <sup>d</sup> Model 3: in addition to the factors noted in model 2, also adjusted for mode of delivery.

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