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Maternal Infections during Pregnancy and Cerebral Palsy: A Population-based Cohort Study

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Abstract

Background—Cerebral palsy (CP) is a common motor disability in childhood. We examined the association between maternal infections during pregnancy and the risk of congenital CP in the child.

Methods—Liveborn singletons in Denmark between 1997 and 2003 were identified from the Danish National Birth Registry and followed from 1 year of life until 2008. Redemption of antibiotics from the National Register of Medicinal Product Statistics and maternal infections reported by the National Hospital Register were used as markers of maternal infection during pregnancy. CP diagnoses were obtained from the Danish Cerebral Palsy Registry. Adjusted hazard ratio (HR) and 95% confidence interval (CI) were estimated by Cox proportional hazard models.

Results—Of the 440 564 singletons with follow-up data, 840 were diagnosed with congenital CP. Maternal genito-urinary tract infections (HR 2.1, 95% CI 1.4, 3.2) were associated with CP in all births, in term births (HR 1.9, 95% CI 1.1, 3.2), in children with spastic CP (HR 2.1, 95% CI 1.4, 3.3), and among first-born children (HR 1.9, 95% CI 1.4, 3.3). Overall, we found associations between redeemed nitrofurantoin (HR 1.7, 95% CI 1.1, 2.8) and CP. Among trimester-specific exposures, CP risk was associated with prescriptions redeemed in the first trimester for any antibacterials, beta-lactam antibacterials, and nitrofurantoin, an antibiotic commonly used to treat lower urinary tract infection, and genito-urinary tract infections in the third trimester.

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Conclusion—Genito-urinary tract infections and antibiotic use during pregnancy were associated with increased risks of CP, indicating that some maternal infections or causes of maternal infections present in prenatal life may be part of a causal pathway leading to CP.

Keywords

maternal infections; bacterial infections; pregnancy; congenital cerebral palsy

Background

Cerebral palsy (CP) is one of the most common motor disabilities in childhood with prevalence estimates close to 2 per 1000 livebirths in Denmark.[1,2] Fetal exposures during gestation, such as maternal infections, have been associated with an increased risk for CP and other neurological disorders in the child.[3-10] Part of the immune response to infections is the possible increase of brain vulnerability, which may cause fetal white matter damage, identified as an important risk factor for the development of CP in preterm infants. Gestational age may modify the potential effect or act as a mediator on the causal pathway from infection to CP, inasmuch as intrauterine infection/inflammation has been identified as a cause of preterm delivery.[12] Less is known about the potential effects in term infants.[4,5]

Neurological outcome studies often focus on inpatient hospital-diagnosed infections with less attention given to infections diagnosed by primary care doctors outside of hospitals, or in outpatient clinical settings. Prescription data, as a marker of infection, provide the ability to study infections not requiring hospitalisation otherwise excluded from hospital-based studies.

We hypothesised that exposure to some maternal infections during pregnancy may increase the risk of CP. We investigated a wide range of maternal infections or markers of maternal infections occurring during pregnancy in a population-based cohort.

Methods

Residents in Denmark are assigned a unique personal identification number that enables linkage of individual data among all national registries.[13] From the Danish National Birth Registry we identified all liveborn singletons born in Denmark between January 1997 and December 2003 who were alive at birth and resided in Denmark up to December 2008 (n = 442 370). Of these, 440 564 survived to 1 year after birth and were included in the analysis (Figure 1).

Exposure information

In Denmark, the general practitioner (GP) provides primary medical care but refers patients to a specialist or hospital, either for inpatient or for outpatient care, if conditions warrant specialised attention. GPs, other physicians, or dentists can prescribe medication and all pharmacy-redeemed prescriptions are recorded in a national prescription register.[14] We identified maternal infections by two separate sources, the National Register of Medicinal Product Statistics (prescription registry) and the Danish National Hospital Register, in order to study a wide spectrum of maternal infections.

Redeemed antibiotics

The prescription registry was used to capture maternal infections treated with prescription antibiotics; infections treated only intravenously or during an inpatient hospital admission are not recorded in the registry. Data on type of infection, reason for prescription (treatment or prophylaxis), and actual use of medication are not available. The prescription registry contains individual-level information on all redeemed prescriptions in Denmark since 1994 except on drugs sold without a prescription or drugs for inpatient use only. Drugs are coded according to the WHO Anatomical Therapeutic Chemical (ATC) classification system. ATC codes and date of sale for each prescription are stored when redeemed.

Antibiotics for the study were defined with the overall ATC code ‘J01’ (any systemic antibacterial), and the ATC subgroups ‘J01C’ (beta-lactam antibacterials, penicillins), ‘J01E’ (sulfonamides and trimethoprim), ‘J01F’ (macrolides, lincosamides, and streptogramins), and ‘J01X’ (other antibacterials). We investigated the specific antibiotics ‘J01CE02’ (phenoxymethylpenicillin) and ‘J01FA01’ (erythromycin) because of their frequent use, and ‘J01CA08’ (pivmecillinam), ‘J01EB02’ (sulfamethizole, mono-therapy not in combination with trimethoprim), and ‘J01XE01’ (nitrofurantoin), which are used almost exclusively to treat uncomplicated lower urinary tract infections in Denmark.[15]

We categorised children as exposed to redeemed antibiotics during pregnancy if the mother redeemed a prescription for an aforementioned medication with the date of sale between the start of pregnancy and the date of birth of the child.

Hospital-reported maternal infections

The Danish National Hospital Register was used to capture all maternal infections diagnosed and treated during inpatient or outpatient hospital admission; information on diagnoses by GPs is not yet available. The register may include infections treated with either oral or intravenous medications. The register holds information on all discharges from Danish hospitals including outpatient treatments. Diagnostic information is based on the Danish version of the International Classification of Diseases, 10th revision (ICD-10), from 1994 onward and reported to the register after each hospital visit.

We categorised children as exposed to hospital-reported maternal infections during pregnancy if the mother was recorded in the register with an ICD-10 code for a defined infection between the start of pregnancy and the date of birth of the child (see Appendix 1).

Cerebral palsy

Children’s CP status was ascertained from the Danish Cerebral Palsy Registry. Cohort members were identified as having *validated congenital CP* if alive after the first year of life and included in the registry. The population-based registry contains records of individuals with CP from the birth year 1925 and reported prevalence data since 1950 for part of the country.[1] The registry covers the entire country from birth years 1997–2003. Case notes are collected from all paediatric departments and suspected cases of CP are validated based on a review of a child’s physical findings at the age of 5–6 years contained in medical records by trained child neurologists and obstetricians. Information including subtyping of CP is

registered in a standard format.[1] Resolved conditions, progressive disorders, motor disorders attributable to spinal cord diseases, and cases with obvious post-perinatal aetiology are excluded from the registry. Time of onset was defined in the cohort as the first recorded date of diagnosis (i.e. the date diagnosis criteria were met), corresponding with the date parents were informed of a confirmed CP diagnosis. If the date of diagnosis occurred before the age of 1 because of a firm diagnosis (n = 209) or was missing (n = 17), the time of onset was defined as 1 year after the date of birth.

Covariates

Data on maternal age, gestational age at birth, sex, smoking status during pregnancy, mode of delivery, parity, and birth year were obtained from the Danish Medical Birth Registry. During the study years, data on gestational age at birth were estimated from ultrasound measures during early pregnancy, and if not available, the last menstrual date was used (<1%). Parental income was obtained from the Fertility Database, which contains annually collected education, employment, and family/housing information for people of fertile age in Denmark.[16] Parental income was defined as the parents' combined income during the child's birth year; if missing for both parents, data from the previous calendar year were used if available.

Statistical analyses

We modelled the risk of CP in the children over time among different exposure groups during pregnancy. Children were categorised as unexposed if the mother did not have a redeemed prescription for any systemic antibiotic (ATC: J01) and did not have an ICD-10 code for any of the defined infections between the start of pregnancy and the date of birth of the child. Initiation of pregnancy was calculated by subtracting gestational age in days from the date of birth. All children included in the analysis survived to 1 year of age and were followed until a reported diagnosis of CP in the Cerebral Palsy Registry, death, or December 2008, whichever occurred first. Hazard ratio (HR) and 95% confidence interval (CI) were estimated by Cox proportional hazard models with person-years as the time-to-event variable and robust standard errors accounted for interdependency between multiple pregnancies of women during the study period [n = 103 582 mothers (31.5%) had multiple pregnancies]. Directed acyclic graphs[17] provide a method for the evaluation of confounders and mediators, and were used to guide the selection of potential confounders to be controlled. Factors associated with an increased risk for CP as well as for infection were considered potential confounders; factors associated with an increased risk for CP but possibly affected by infection (mediators), i.e. intrauterine growth restriction, were not considered confounders. The final models included maternal age[18] (<20, 20–24, 25–29, 30–34, >= 35), smoking during pregnancy[19] (yes, no), income during birth year[20] (<300 000, 300 000–500 000, and >500 000 Danish kroner), and the midpoint calendar year from all birth years[2] (<2000 and ≥2000). Missing values for smoking and income (<5%) were included as distinct categories to maintain the sample size.

We performed a number of stratified analyses. First, to examine the potential modifying effect of gestational age on the association, we performed analyses among children born preterm (<37 weeks) or term (≥37 weeks), knowing that stratifying on a potential collider

variable could introduce bias by inducing otherwise controlled associations.[21] Second, we restricted cases in our analysis to those with spastic CP, a common subtype that appears to be associated with intrauterine infection.[22] Third, we categorised timing of maternal infection during pregnancy based on the trimester in which a prescription was redeemed or a defined ICD-10 code infection reported. The time of maternal infection was assigned to the trimester(s) in which a prescription was redeemed or an ICD code reported because the actual start and end date of the infections are not available. For each trimester, exposure groups were compared with the unexposed group used in the original analysis. Only children who were exposed during the trimester of interest were included in the trimester-specific analysis. One-third of children were exposed during multiple trimesters and included in the analysis for each exposed trimester. Fourth, we looked at the overall associations in firstborn children to eliminate possible bias related to behaviour modification induced by previous adverse pregnancy outcomes if a suspect prenatal exposure is considered harmful and is modifiable.[23] Lastly, we categorised women by the number of redeemed prescriptions to examine the association of possible severity or length of maternal infection and CP. A stratified analysis by the number of hospital diagnoses was not performed because recurrent infections or the same infection recorded on different dates could not be distinguished in our data. Analyses were performed using PROC PHREG in SAS version 9.2 (SAS Institute, Cary, NC, USA). The study was approved by the Danish Data Protection Agency.

Results

Children were followed from 1 year to a maximum of 12 years of age (mean 8.5 years of age). A total of 840 children with CP were identified, of whom 86% (n = 720) had spastic CP. Exposure and case status are illustrated in Figure 1. Table 1 summarises characteristics of cohort children who had mothers exposed to any redeemed antibiotic or any hospital-reported maternal infection during pregnancy. Thirty per cent of children had mothers with a redeemed antibiotic during pregnancy and 3% of children had mothers who had a hospital-reported maternal infection; 6.7% of exposed children were exposed to mothers with both a redeemed antibiotic and a hospital-reported maternal infection during pregnancy. Women with hospital-reported maternal infections during pregnancy were slightly younger and had lower incomes, lower gestational age, more caesarean sections, and later birth years, and more reported they had smoked during pregnancy, compared with unexposed women.

Children of mothers with any redeemed antibiotic or hospital-reported maternal infection during pregnancy were more likely to have CP than unexposed children (Table 2). An increased risk of CP was observed with children whose mothers redeemed nitrofurantoin (HR 1.7, 95% CI 1.1, 2.8) and with hospital-reported maternal genito-urinary tract infection (HR 2.1, 95% CI 1.4, 3.2). Fewer than five CP cases had mothers with amniotic sac and membrane infections (results given in the table).

Among the subgroup of children of mothers exposed to both any redeemed antibiotic and any hospital-reported maternal infection during pregnancy, we observed an association with CP (HR 1.7, 95% CI 1.2, 2.5) (data not shown).

Analysis of spastic CP cases revealed statistically significant associations between exposure to any hospital-reported maternal infection (HR 1.6, 95% CI 1.1, 2.2), hospital-reported maternal genito-urinary tract infections (HR 2.1, 95% CI 1.4, 3.3), and spastic CP (data not shown).

In the analyses stratified on gestational age, among unexposed children, the percentage of children born preterm with CP was 1.1% (154/13 717), notably higher than the percentage of children born term with CP (0.13%; 387/289 413) (Table 3). Among children born preterm, 32% were exposed to redeemed antibiotics and 9% to hospital-reported maternal infections during pregnancy, whereas in children born at term, 30% were exposed to redeemed antibiotics and 4% to hospital-reported maternal infections during pregnancy. Among children born preterm, no statistically significant associations were observed between hospital-reported maternal infections and the risk of CP; however, for some exposure groups, stratum-specific numbers were small and CI wide. Among children born at term, statistically significant associations with CP were observed among those exposed to any redeemed antibiotic, beta-lactam antibacterials, phenoxymethylpenicillin, and hospital-reported maternal genito-urinary tract infection (Table 3).

When examining the timing of exposure, first trimester exposure to any redeemed antibiotic, betalactam antibacterials, or nitrofurantoins (other antibacterials were predominately nitrofurantoin) was associated with CP (Table 4, limited data presented). Exposures during the second or third trimester for these medications were not significantly associated with CP, although exposure to any redeemed antibiotic during the second trimester was significantly associated with CP (HR 1.3, 95% CI 1.1, 1.5). Third trimester diagnosis of any hospital-reported maternal infections (HR 1.8, 95% CI 1.2, 2.8) and hospital-reported maternal genito-urinary tract infection (HR 2.5, 95% CI 1.6, 4.1) was associated with CP.

Our analysis in firstborn children showed associations between CP and exposure to redeemed nitrofurantoin (HR 2.3, 95% CI 1.3, 4.1) and hospital-reported genito-urinary infections (HR 1.9, 95% CI 1.1, 3.4) (data not shown).

Sixty-six per cent of women who redeemed antibiotics during pregnancy redeemed only one prescription and 34% redeemed >1 prescription during pregnancy. No additional risks associated with the redemption of >1 prescription were observed (any antibacterials HR 1.2, 95% CI 0.9, 1.5) (data not shown).

Comment

Overall, we found CP to be associated with markers of maternal infection, specifically a redeemed prescription for any antibacterial medication or nitrofurantoin during pregnancy and hospital-reported maternal genito-urinary tract infections. These associations may be causal, indicators of causes (e.g. immune factors),[24] or non-causal.

Several studies support relations between intrauterine infection and the development of periventricular leukomalacia,[25-27] which is typically found in children with spastic CP, children who were preterm, and occasionally children who were term.[28] The immune response to infections, including the release of cytokines, may be an aetiologic factor for

encephalopathy and possible CP leading to white matter brain damage by affecting fetal blood flow or the haemo-static system, coagulation necrosis of white matter,[29] and increased permeability of the blood–brain barrier (facilitating microbial products and cytokines passing into the brain).[30] Our associations of maternal infections with spastic CP are not new and are consistent with previous research.

Statistically significant associations between our markers for maternal infection and CP were not observed among children born preterm, which is expected if gestational age is an intermediate variable in the causal pathway. A higher exposure rate among preterm than term births supports maternal infection as a risk factor for preterm births, and the association between preterm birth and CP overall indicates that preterm birth could be a mediator, or modifier, of the association between maternal infection and CP. If so then our stratified analyses on preterm birth may hide the causal association of interest.

Several studies in preterm infants have examined the association between maternal infection with elevated cytokine levels and white matter damage in infants, but few studies exist in term infants that link elevated maternal cytokine levels to neurological disorders in the offspring.[31] Our results in term children support such an association and are consistent with results from two population-based case-control studies: Neufeld *et al.* found an increased risk of CP among term infants of women with any infection during hospitalisation for delivery,[5] and Grether and Nelson found an increased risk of CP in normal birthweight infants exposed to intrauterine maternal infection.[7]

Depending on the trimester, we found associations with particular markers for maternal infection and the risk of CP. Timing of infections may be an important component of fetal brain development, and our results indicate that some maternal infections may operate early in gestation; for example, chorioamnionitis may increase risk in the second trimester and be linked to preterm birth, whereas genito-urinary infections later in pregnancy may play a role in CP risk. Small strata and wide CI in this subanalysis affect our ability to know if other associations are present that could help clarify underlying associations between maternal infections in particular trimesters and CP. Our results on timing are only suggestive considering that the true onset of infection and the time of diagnosis may differ in that an infection could have been present for some time prior to presentation for care.

The frequency of genito-urinary tract infections in pregnancy,[32] their proximity to the fetus, and their association with other childhood neurological outcomes[9,33] provide reason for investigation in perinatal studies. The prescription data source does not include the indication for treatment; however, in Denmark nitrofurantoin, pivmecillinam, and sulfamethizole (monotherapy) (other sulfonamides and trimethoprim antibiotics are contraindicated in pregnancy[34,35]) are used almost exclusively to treat lower urinary tract infections and are not normally used for other indications during pregnancy.[15] A comparison of these drugs, used for the same infection but with different mechanisms of action, may provide new information. The risk of CP associated with nitrofurantoin may suggest direct effects on the fetal brain, whereas the statistically non-significant risk associated with pivmecillinam and sulfamethizole may be attributable to better treatment effects, less severe underlying disease, or chance findings.

We investigated all antibiotics on the Danish market, thus including a range of very different pharmacokinetic and dynamic antibiotics. If side effects from the antibiotics are responsible for the associations between antibiotics and CP, we may expect to see largely different associations across the antibiotics, corresponding to the different chemical structures. However, the relatively similar associations across different antibiotics seem more likely related to an underlying cause or infection.

Hospital-reported infection diagnoses suggest more severe infection compared with the prescription data; our results reflect this in that we see higher HRs for CP among children exposed to hospital-reported maternal infection. Lower HRs among the prescription data may reflect the antibiotic's effect to treat infection, thus removing the causal factor and biasing estimates toward the null, or exposure misclassification. Misclassification (non-differential or differential) of the prescription and hospital data is possible and could potentially bias our effect estimates in either direction. Misclassification of the prescription data could occur if women categorised as unexposed to antibiotics used antibiotics redeemed outside the pregnancy time period or if women categorised as exposed to antibiotics used them as prophylactic treatment or were misdiagnosed and never actually infected. Women with redeemed antibiotics may not take them, but this would only affect estimates if the underlying exposure differed from the categorised exposure. Misclassification of the hospital data may occur if women categorised as unexposed had undiagnosed infections (e.g. mild viral infections) or if women with diagnosed infections were actually uninfected. Women with complicated pregnancies may be seen more frequently than women without complications, which may increase their likelihood of being diagnosed with an infection or of receiving prophylactic antibiotics. Given our method of identifying maternal infections, some of these misclassifications and biases are unavoidable. To potentially reduce some bias, we considered the number of redeemed prescriptions, assuming >1 may indicate actual use or infection and therefore a better marker of maternal infection. No additional risk was observed among the 30% of women with >1 redeemed prescription.

Our study has several strengths, including well-maintained population-based registries, minimal loss to follow-up, well-documented redeemed prescription data, reliable hospitalisation information, and physician-validated CP cases. The use of data collected for non-research purposes may reduce the risk of differential misclassification. Redeemed prescription data provides the ability to study indication-specific antibiotics and an expanded exposure group that includes non-hospitalised maternal infections. In terms of limitations, subclinical maternal infections or infections not requiring hospitalisation or prescribed antibiotics may not have been captured in our data sources. The small number of exposed cases for some of the strata limits interpretation of the findings. Children must survive 1 year of age to be included in the CP registry. Therefore, our results are conditional on survival past 1 year, which would bias results if a disproportionate amount of potential CP cases, as compared with children without CP, do not survive 1 year of age, a condition that at present cannot be confirmed. We could not adjust for unknown or unmeasured social and biological factors that may explain some of the increased risk.

This study supports that certain maternal infections during pregnancy and their causes or consequences may have a potential effect on fetal brain development.[36] Our results reflect

the complexity of the aetiologic processes leading from infection to CP. Future research should explore the timing of exposure to infection, a larger set of specific biomarkers of infections, and information on indirect conditions linked to infections.

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Appendix 1 - Definitions of infection categories based on ICD-10 codes

Any hospital infection during pregnancy	Includes all following ICD-10 codes
Certain infectious and parasitic diseases (generally recognised as communicable or transmissible diseases)	A00-B99
Infections of genito-urinary tract in pregnancy	O23
Maternal infectious and parasitic diseases classifiable elsewhere but complicating pregnancy, childbirth, and the peurperium	O98
Infection of amniotic sac and membranes	O41.1
All other hospital infections (eye, ear, central nervous system, upper airway, pneumonia, etc.)	See below table

Complete list of 'all other infections' category:	
Infection in the central nervous system	G00-G02, G04-G07
Eye infections	H00-H01, H03, H040, H043, H10, H16
Ear infections	H60, H62, H65-H68, H70, H75
Upper airway infections	J00-J06
Pneumonia and influenza	J09-J18, J20-J22
Abscess in thorax	J85-J86
Stomatitis, glossitis	K12, K14
Appendicitis	K35, K379
GI abscess	K61
Peritonitis	K650
Cholescystitis	K810
Liver abscess	K750
Skin infections	L00-L08
Infections of joints (excluding common inflammatory)	M00-M01
Infective myositis	M600
Osteomyelitis	M860-M862, M869
Kidney infections	N10, N129
Cystitis	N30
Genital infections	N70-N77

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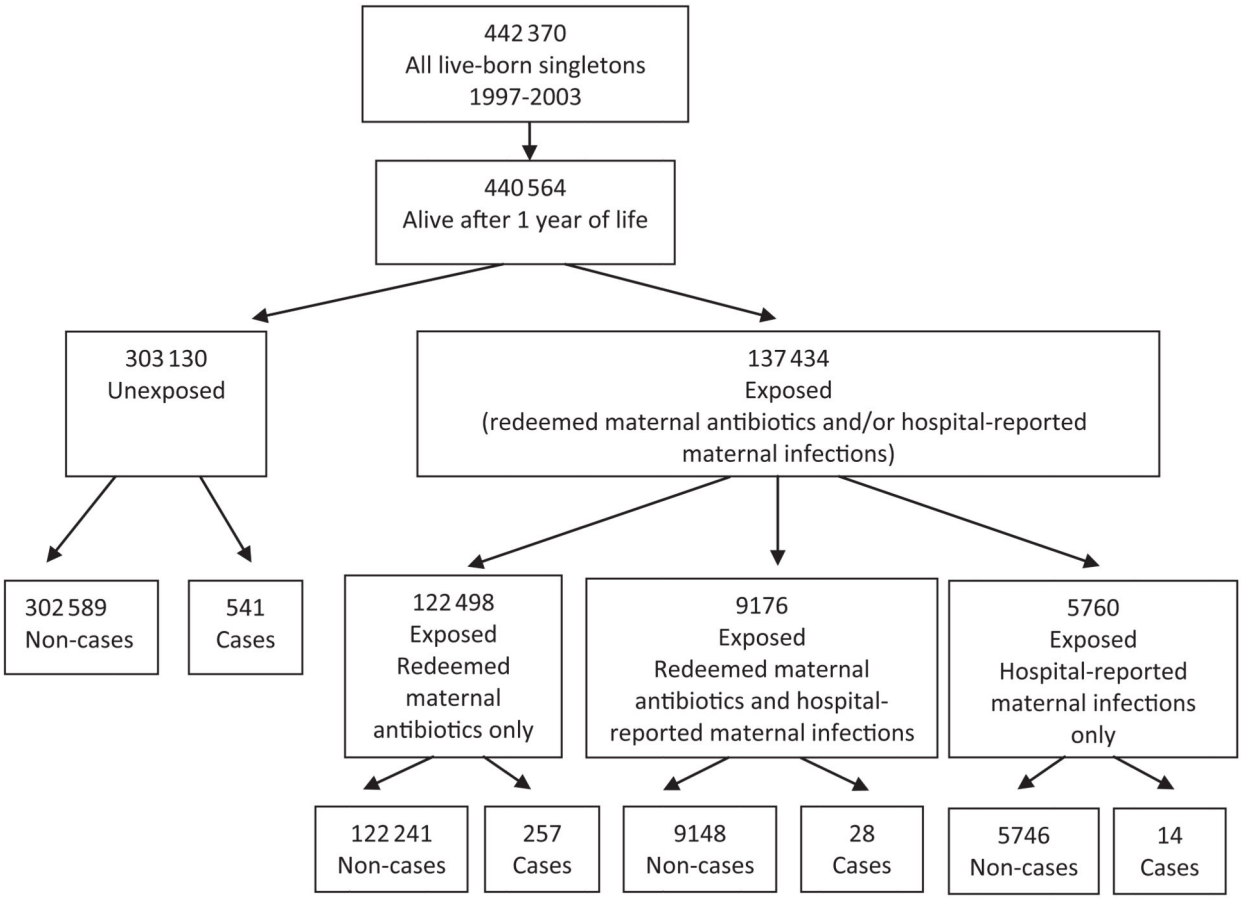

Cases by exposure status

		Hospital-reported maternal infections: Yes	No	Total
Redeemed maternal antibiotics	Yes	28	257	285
	No	14	541	555
	Total	42	798	840

Figure 1.

Exposure and case status of the study population. The exposure classification and case status of the study population is presented as a flow chart with a table of the exposure classification of children with cerebral palsy.

Table 1

Baseline characteristics of all children born in Denmark from 1997 to 2003 who survived to 1 year of age, classified by the mother's exposure to redeemed antibiotics or hospital-reported maternal infections

	Unexposed		Exposed to redeemed antibiotics		Exposed to hospital-reported maternal infection	
Characteristic	**Number**	**%**	**Number**	**%**	**Number**	**%**
Gender						
Male	155 535	51	67 500	51	7 679	51
Female	147 595	49	64 174	49	7 257	49
Missing	0	0	0	0	0	0
Gestational age (weeks)						
<37	13 717	5	6 374	5	1 300	9
37–42	263 282	87	114 283	87	12 602	84
≥42	26 131	9	11 017	8	1 034	7
Missing	0	0	0	0	0	0
Income[a]						
Low	50 782	17	25 345	19	3 832	26
Medium	135 232	45	59 955	46	6 407	43
High	110 522	36	42 885	33	4 072	27
Missing	6 594	2	3 489	3	625	4
Maternal age (years)						
<20	4 265	1	2 818	2	592	4
20–24	37 711	12	19 538	15	3 038	20
25–29	111 563	37	46 648	35	5 134	34
30–34	104 080	34	43 746	33	4 326	29
≥35	45 511	15	18 924	14	1 846	12
Missing	0	0	0	0	0	0
Smoking during pregnancy						
No	231 393	76	92 757	70	10 064	67
Yes	58 750	19	33 082	25	4 078	27
Missing	12 987	4	5 835	4	794	5
Caesarean delivery						
No	246 446	81	104 572	79	11 275	75
Yes	56 684	19	27 102	21	3 661	25
Missing	0	0	0	0	0	0
Birth year						
1997–1999	133 263	44	55 816	42	5 829	39
2000–2003	169 867	56	75 858	58	9 107	61
Missing	0	0	0	0	0	0

The exposure groups are not mutually exclusive and may include overlap; see the Results section for the exact percent.

[a]Low income was defined as <300 000 Danish kroner, middle income as 300 000–500 000, and high income as >500 000.

Table 2

Hazard ratios (HR) for cerebral palsy (CP) according to markers of infection during pregnancy

	Total *N*	CP cases	HR[a] (95% confidence interval)
Redeemed antibiotics			
Unexposed	303 130	541	1.0 [Reference]
Any antibacterial for systemic use	131 674	285	1.2 [1.0, 1.4]
Beta-lactam antibacterials	102 279	212	1.2 [1.0, 1.4]
Phenoxymethylpenicillin	58 525	124	1.2 [1.0, 1.4]
Pivmecillinam[b]	27 703	50	1.0 [0.8, 1.4]
Sulfonamides and trimethoprim	29 895	70	1.3 [1.0, 1.6]
Sulfamethizole, mono therapy[b]	29 679	70	1.3 [1.0, 1.6]
Macrolides, lincosamides, and streptogramins	15 235	35	1.3 [0.9, 1.8]
Erythromycin	11 734	25	1.2 [0.8, 1.7]
Other antibacterials	5 516	16	1.6 [1.0, 2.7]
Nitrofurantoin[b]	5 403	16	1.7 [1.1, 2.8]
Hospital-reported maternal infections			
Unexposed	303 130	541	1.0 [Reference]
Any hospital-reported maternal infection	14 936	42	1.6 [1.1, 2.1]
Certain infectious and parasitic diseases (A00-B99)[c]	3 284	6	1.0 [0.4, 2.2]
Infections of genito-urinary tract in pregnancy (O23)	6 231	24	2.1 [1.4, 3.2]
Maternal infectious and parasitic diseases classifiable elsewhere but complicating pregnancy, childbirth, and the peurperium (O98)	406	1	1.4 [0.2, 9.7]
Infection of amniotic sac and membranes (O41.1)	260	2	4.0 [1.0, 16.1]
All other hospital infections (eye, ear, central nervous system upper airway, pneumonia, etc.)	6 027	11	1.0 [0.5, 1.8]

[a] Adjusted HR adjusted for maternal age, smoking during pregnancy, parental income during birth year, and calendar year.

[b] Medications commonly used for treatment of lower urinary tract infection in Denmark.[15]

[c] Includes diseases generally recognised as communicable or transmissible according to the International Classification of Diseases, 10th revision.

Table 3

Hazard ratios (HR) for cerebral palsy (CP) among preterm or term infants according to markers of infection during pregnancy

	Preterm delivery			Term delivery		
	Total *N*	**CP cases**	**HR[a] (95% CI)**	**Total *N***	**CP cases**	**HR[a] (95% CI)**
Redeemed antibiotics						
Unexposed	13 717	154	1.0 [Reference]	289 413	387	1.0 [Reference]
Any antibacterial for systemic use	6 374	79	1.1 [0.8, 1.4]	125 300	206	1.2 [1.0, 1.4]
Beta-lactam antibacterials	4 850	52	1.0 [0.7, 1.3]	97 429	160	1.2 [1.0, 1.5]
Phenoxymethylpenicillin	2 670	29	1.0 [0.6, 1.5]	55 855	95	1.3 [1.0, 1.6]
Pivmecillinam[b]	1 315	14	1.0 [0.6, 1.7]	26 388	36	1.0 [0.7, 1.5]
Sulfonamides and trimethoprim	1 560	26	1.5 [1.0, 2.2]	28 335	44	1.1 [0.8, 1.6]
Sulfamethizole, mono therapy[b]	1 546	26	1.5 [1.0, 2.2]	28 133	44	1.1 [0.8, 1.6]
Macrolides, lincosamides, and streptogramins	778	9	1.0 [0.5, 2.0]	14 457	26	1.3 [0.9, 2.0]
Erythromycin	591	8	1.2 [0.6, 2.4]	11 143	17	1.1 [0.7, 1.8]
Other antibacterials	269	4	1.4 [0.5, 3.7]	5 247	12	1.7 [1.0, 3.1]
Nitrofurantoin[b]	260	4	1.4 [0.5, 3.8]	5 143	12	1.8 [1.0, 3.1]
Hospital-reported maternal infections						
Unexposed	13 717	154	1.0 [Reference]	289 413	387	1.0 [Reference]
Any hospital-reported maternal infection	1 300	20	1.4 [0.9, 2.2]	13 636	22	1.2 [0.8, 1.8]
Certain infectious and parasitic diseases (A00-B99)[c]	214	3	1.2 [0.4, 3.8]	3 070	3	0.7 [0.2, 2.3]
Infections of genito-urinary tract in pregnancy (O23)	645	10	1.4 [0.7, 2.7]	5 586	14	1.9 [1.1, 3.2]
Maternal infectious and parasitic diseases classifiable elsewhere but complicating pregnancy, childbirth, and the peurperium (O98)	32	1	3.0 [0.4, 20.4]	374	0	-
Infection of amniotic sac and membranes (O41.1)	142	2	1.2 [0.3, 4.9]	118	0	-
All other hospital infections (eye, ear, central nervous system, upper airway, pneumonia, etc.)	431	5	1.0 [0.4, 2.5]	5 596	6	0.8 [0.4, 1.8]

CI, confidence interval.

[a] Adjusted HR adjusted for maternal age, smoking during pregnancy, parental income during birth year, and calendar year.

[b] Medications commonly used for treatment of cystitis in Denmark.[15]

[c] Includes diseases generally recognised as communicable or transmissible according to the International Classification of Diseases, 10th revision.

Table 4

Hazard ratios (HR) for cerebral palsy (CP) among all children according to trimester of exposure for any redeemed antibiotic and any hospital-reported maternal infection during pregnancy

	First trimester			Second trimester			Third trimester		
	Total *N*	CP cases	HR[a] (95% CI)	Total *N*	CP cases	HR[a] (95% CI)	Total *N*	CP cases	HR[a] (95% CI)
Unexposed	303 130	541	1.0 [Reference]	303 130	541	1.0 [Reference]	303 130	541	1.0 [Reference]
Any antibacterial for systemic use	52 707	129	1.3 [1.1, 1.6]	62 878	143	1.3 [1.1, 1.5]	48 798	88	1.0 [0.8, 1.3]
Any hospital-reported maternal infection	3 663	9	1.4 [0.7, 2.6]	6 487	17	1.4 [0.9, 2.3]	6 913	23	1.8 [1.2, 2.8]

Children who were not exposed during the trimester of interest were excluded from the analysis for that specific trimester. Children born before the third trimester were not included in the third trimester analysis. Children may have been exposed for more than one trimester.

CI, confidence interval.

[a]Adjusted HR adjusted for maternal age, smoking during pregnancy, parental income during birth year, and calendar year.