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This is a Non Peer Reviewed Manuscript version of the following article, accepted for publication in *Annals of Internal Medicine*.

2023-11-27

Pregnancy outcomes in women with a prior cervical intraepithelial neoplasia grade 3 diagnosis : a nationwide population-based cohort study with sibling comparison design

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Ann Intern Med. 2022 Feb;175(2):210-218.

American College of Physicians

<http://doi.org/10.7326/M21-2793>

<http://hdl.handle.net/10616/48901>

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2 **Pregnancy outcomes in women with a prior cervical intraepithelial neoplasia**
3 **grade 3 diagnosis: a nationwide population-based cohort study with sibling**
4 **comparison design**

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28 **Abstract**

29 **Background:** Treatment of cervical intraepithelial neoplasia grade 3 (CIN3) removes or destroys
30 part of the cervix and might subsequently influence pregnancy outcomes.

31 **Objective:** To investigate pregnancy outcomes in women diagnosed with CIN3.

32 **Design:** Population- and sibling-matched cohort study.

33 **Setting:** Sweden, 1973-2018.

34 **Participants:** General population comparison included 78 450 singletons born to women
35 diagnosed with CIN3 and 784 500 matched singletons born to women in the general population
36 who had no CIN3 diagnosis; sibling comparison included 23 199 singletons born to women
37 diagnosed with CIN3 and 28 135 singletons born to their sisters without a CIN3 diagnosis;

38 **Measurements:** Preterm birth, including spontaneous or iatrogenic preterm birth; Infection-
39 related outcomes, including chorioamnionitis and infant sepsis; and early neonatal death, defined
40 as death during the first week after birth.

41 **Results:** Compared with the matched general population, women previously diagnosed with
42 CIN3 were more likely to have a preterm birth especially extremely preterm (22-28 weeks; OR,
43 3.00; 95% CI, 2.69-3.34) and spontaneous preterm (OR, 2.12; 95% CI, 2.05-2.20) birth,
44 infection-related outcomes including chorioamnionitis (OR, 3.23; 95% CI, 2.89-3.62) and infant
45 sepsis (OR, 1.72; 95% CI, 1.60-1.86), and early neonatal death (OR, 1.83; 95% CI, 1.61-2.09).
46 Sibling comparison analyses rendered largely similar results. Over time the risk difference
47 attenuated for all outcomes and disappeared for early neonatal death.

48 **Limitations:** Lack of data on CIN3 treatment and spontaneous abortion.

49 **Conclusion:** Prior history of CIN 3 is associated with adverse pregnancy outcomes even after
50 accounting for familial factors. Decreasing risk estimates over time suggest that adverse

51 pregnancy outcomes among women diagnosed with CIN3 may be minimized by improving
52 treatment modalities.

53 **Primary Funding Source:** Swedish Research Council, Swedish Cancer Society, and FORTE.

54 **Introduction**

55 The ‘screen-and-treat strategy’, as recommended by the World Health Organization, is
56 increasingly being adopted in low-income countries to increase treatment after a positive
57 screening for high-grade cervical intraepithelial neoplasia (CIN) (1). Low costs, decreased
58 patient anxiety, and increased compliance make the ‘screen-and-treat strategy’ appealing (2).
59 However, overtreatment has been reported to range from 13% to 83% when treating a high-grade
60 CIN without additional biopsy confirmation (2). Also in countries with population-based
61 screening programs and extensive colposcopy services, at least 6 treatments of CIN are estimated
62 to be made to prevent one case of cervical cancer (3). Overtreatment of women of reproductive
63 age is of significant public health concern, given that removal or destruction of the cervix could
64 compromise its function and subsequently affect future pregnancy outcomes (4-7).

65 Observational studies and meta-analyses have linked treatment for cervical intraepithelial
66 neoplasia grade 3 (CIN3) with increased risk of subsequent preterm delivery and related
67 outcomes (4, 7-11). However, comparisons in previous studies were limited to the general
68 population or births delivered within the same hospital (12, 13), and have not accounted for
69 familial factors. Therefore, these studies may be confounded by unmeasured factors shared
70 within families (e.g., common gene (14), similarity in lifestyle (15), and other risk factors) as
71 both CIN3 and adverse pregnancy outcomes have been reported to aggregate within families (16,
72 17).

73 Using data from 4.6 million Swedish births over a 46-year period (1973-2018), this study
74 investigated 1) the association between CIN3 and future preterm birth and birth-related
75 outcomes, while adjusting for familial factors through a sibling comparison analyses; 2) the
76 potential effect of calendar period on pregnancy outcomes; and 3) whether these associations
77 could be modified by maternal characteristics.

78 **Methods**

79 **Data sources**

80 Our study used data from five linked data sources. The Swedish Medical Birth Register
81 contains detailed information on all births in Sweden since 1973, including reproductive history
82 and demographic data of the mother, pregnancy outcomes, and complications during pregnancy,
83 delivery and the neonatal period (18). The Swedish Cancer Register includes histological
84 classification of malignant and premalignant lesions (CIN3) of the cervix since 1958 (19). The
85 Swedish Multi-Generation Register provides information on all first-degree relatives for
86 individuals born in Sweden since 1932 (20). The Swedish Education Register contains
87 information on the highest attained educational level and is continuously updated. The Swedish
88 Total Population Register includes life events such as birth, death, emigration, and marital status
89 of all Swedish residents since 1968 (21). All these registers cover the total population of Sweden
90 and are of very high quality (18-20). Record-linkage between the registers was made using the
91 Personal Identification Number- a unique identifier assigned to all residents in Sweden (22).

92 The study was approved by the Regional Ethical Review Board in Stockholm, Sweden
93 (Approval No.: 2012/217/-32/2).

94 **Study population**

95 A total of 4 629 931 singleton births with known gestational age were reported to the
96 Medical Birth Register between 1973 and 2018. Among them, we identified 78 450 births after a
97 maternal CIN3 diagnosis, which was achieved by linking to the Swedish Cancer Register to
98 identify the date of CIN3 diagnosis (ICD-7 code 171; WHO C24 code 144) (19, 23). Using an
99 optimal matching algorithm(24) (fullmatch function in R package “DOS2”), we matched the 78
100 450 births to 784 500 births to women without CIN3 diagnosis (**Supplement Figure 1**, available
101 at Annals.org). This algorithm used exact match on calendar period of delivery, age at delivery,

102 and Swedish healthcare region, and optimal close match on years of education, country of birth,
103 preeclampsia diagnosis, marital status, parity, pre-pregnancy body mass index, and smoking in
104 early pregnancy(24).

105 By linking to the Multi-Generation Register(20), we performed a sibling matching by
106 including only births for women diagnosed with CIN3 who had a parous full sister without a
107 CIN3 diagnosis. For a given matched set of sisters, we identified the age when any of the sisters
108 developed CIN3, and excluded all births of sisters before that age (if there was more than one
109 sister who developed CIN3, the oldest age at CIN3 was used). As a result, the sibling comparison
110 analyses included 23 199 births to women with a previous CIN3 diagnosis, and 28 135 births by
111 their CIN3-free sisters (**Supplement Figure 1**, available at [Annals.org](https://www.annals.org)).

112 **CIN3**

113 The exposure was defined as any CIN3 diagnosed before the start of pregnancy (date of birth
114 minus gestational age in days). All women diagnosed with CIN3 were considered to have been
115 treated, given that biopsy-verified CIN3 has always been treated in Swedish practice. An audit of
116 the Swedish cervical screening program revealed no case of untreated CIN3 among the 1 230
117 women diagnosed with cervical cancer between 1999 and 2002 (25, 26).

118 **Preterm birth and related outcomes**

119 All pregnancy outcomes were derived from the Medical Birth Register, including extremely
120 (≤ 27 weeks), very (28-31 weeks) and moderately (32-36 weeks) preterm birth, chorioamnionitis
121 (ICD-9, 658.4; ICD-10, O411), and infant sepsis (ICD-8, 038; ICD-9; 038, 771.81, 771.83; ICD-
122 10, A40-A42, P36). Preterm birth was further classified as spontaneous or iatrogenic, based on
123 labor onset. Small for gestational age was defined as a birth weight less than 2 standard
124 deviations (SD) below the mean weight for gestational age and gender, according to Swedish

125 birth weights (27). Intrauterine fetal death was defined as a stillbirth delivered at any gestational
126 age (154-321 days in our study population). Early neonatal death was defined as death during the
127 first week after birth.

128 **Covariates**

129 The following covariates were identified from the Medical Birth Register: calendar period of
130 delivery, Swedish healthcare region, maternal age at delivery, parity, diagnosis of preeclampsia
131 (ICD-8: 637; ICD-9: 642E, 642F, 642G; ICD-10: O14, O14), smoking during early pregnancy,
132 and pre-pregnancy body mass index (BMI). BMI was calculated from information on weight and
133 height at the first antenatal care visit (8-12 gestational weeks) (28). Marital status, maternal level
134 of education, and country of birth were obtained from the Medical Birth Register, the Swedish
135 Education Register, and the Swedish Total Population Register, respectively.

136 **Statistical analysis**

137 Conditional logistic regression with robust standard errors (Stata's clogit command) was
138 used in the matched general population comparison analyses to investigate the association
139 between ever having a CIN3 diagnosis and pregnancy outcomes. The analyses were conducted
140 among matched pairs (exact matched for calendar period of delivery, age at delivery, and
141 Swedish healthcare region) and adjusted for years of education, country of birth, preeclampsia
142 diagnosis, marital status, parity, pre-pregnancy body mass index, and smoking in early
143 pregnancy. Conditional logistic regression was also used in the sibling comparison analyses to
144 adjust for common factors shared between sisters.

145 Since treatment modalities for CIN3, as well as obstetrics and neonatal care, have changed
146 profoundly over the last decades, we further stratified the matched general population
147 comparison analyses by year of delivery, to assess the temporal pattern of the association

148 between CIN3 treatment and pregnancy outcomes. To investigate the robustness of our findings,
149 we also conducted additional analyses stratified by years of CIN3 diagnosis.

150 We repeated the matched general population comparison analyses stratified by parity to
151 analyze one birth per woman at a time. To investigate other potential effect modifiers, we also
152 stratified our analyses by maternal age at delivery, years of education, country of birth, marital
153 status, pre-pregnancy BMI, and smoking in early pregnancy.

154 A p-value of <0.05 was considered statistically significant. All statistical analyses were
155 conducted using SAS software, version 9.4 (SAS Institute, Cary, NC, USA) and STATA, version
156 15.1 (STATA, College Station, TX).

157 **Role of the Funding source**

158 The funders had no role in the design of the study; collection, analysis, or interpretation of
159 the data; or the decision to submit the article for publication.

160 **Results**

161 **Population characteristics**

162 The general population comparison included 78 450 births to women with a CIN3 diagnosis
163 and 784 500 matched unexposed births. The CIN3 group and the matched groups are comparable
164 for most variables. The sibling comparison included 23 199 births to women with a CIN3
165 diagnosis and 28 135 births to women without (**Table 1**).

166 **Pregnancy outcomes among women diagnosed with CIN3**

167 Compared with the matched general population, women with a CIN3 diagnosis were 2.09
168 (95% CI, 2.03 – 2.15) times more likely to have a preterm birth (<37 weeks), especially
169 extremely preterm birth (22-28 weeks: OR, 3.00; 95% CI, 2.69 – 3.34) (**Table 2**). Further
170 analyses by labor onset type showed that the association was primarily noted for spontaneous
171 preterm birth, rather than iatrogenic preterm birth. Having a CIN3 diagnosis was also associated
172 with increased risk of infection-related outcomes, including chorioamnionitis and infant sepsis,
173 as well as early neonatal death. We found no difference in the risk of intrauterine fetal death
174 among women with or without a CIN3 diagnosis. Sibling-comparison analyses showed similar
175 associations(**Table 2**).

176 **Pregnancy outcomes among women diagnosed with CIN3, by calendar year**

177 **Figure 1** shows the absolute rate of adverse pregnancy outcomes by CIN3 over time.
178 Compared to the matched general population, women with a prior CIN3 diagnosis were
179 generally more likely to have an adverse pregnancy outcome. However, over time this risk
180 difference attenuated. From 1973-1979 to 2010-2018, the OR (95% CI) decreased from 3.69
181 (3.41 – 3.99) to 1.78 (1.69 – 1.88) for preterm birth (<37 weeks), from 3.51 (2.55 – 4.83) to 1.41
182 (1.23 – 1.62) for infant sepsis, and from 2.46 (1.91-3.19) to 1.12 (0.70-1.79) for early neonatal

183 death (**Figure 2**). Additional analyses by calendar year of CIN3 diagnosis found similar results
184 (**Supplement Figure 2**, available at [Annals.org](#)).

185 **Pregnancy outcomes among women diagnosed with CIN3, by maternal characteristics**

186 **Figure 3** shows stratified analyses by maternal characteristics. In almost all subgroups,
187 women with a prior CIN3 diagnosis were more likely than those without to have a preterm birth,
188 chorioamnionitis, and infant sepsis in almost all subgroups. The associations were stronger
189 among women with a lower education, higher parity, and lower pre-pregnancy BMI compared to
190 their respective counterparts.

191 **Discussion**

192 In this Swedish nationwide population-based study, we found higher preterm birth and
193 related adverse pregnancy outcomes such as chorioamniotitis and infant sepsis among women
194 with a prior CIN3 diagnosis - both compared with the general population of parous women and
195 compared with their parous sisters. The association of CIN3 with many adverse outcomes appear
196 to decrease over time, suggesting that more conservative treatment modalities may minimize
197 subsequent adverse birth outcomes. In particular, early observed associations with neonatal death
198 largely dissipated over time.

199 Previous studies have reported an increased risk of preterm delivery after treatment for CIN3
200 (4, 13). Our study suggests that intrauterine infection may mediate the association between CIN3
201 and adverse pregnancy outcomes, possibly due to a short cervical length after CIN3 treatment
202 (29). Furthermore, the use of over 4.6 million deliveries with sibling comparison design enabled
203 us to study not only extremely severe but rare outcomes (e.g., extremely preterm birth), but also
204 to control for shared familial factors.

205 Our results indicate that caution should be taken when applying a ‘screen-and-treat’
206 approach to women of reproductive age, given that overtreatment of the cervix may have a
207 detrimental effect on future pregnancies. In the context of a ‘screen-and-treat’ strategy in
208 countries where diagnostic resources are limited, treatment is often performed following a
209 positive screening test, without obtaining additional diagnostic confirmation(1). As such, a large
210 proportion of women with low-grade lesions or with a healthy cervix may be treated
211 unnecessarily, which may consequently lead to adverse outcomes in future pregnancies.

212 Overtreatment could also occur if CIN3 is treated with an unnecessarily aggressive surgical
213 procedure, i.e., removing or destroying too much cervical tissue. In our study, the adverse effects
214 of CIN3 treatment on pregnancy outcomes decreased over time, possibly reflecting the change in

215 the surgical procedure. In Sweden, the main CIN3 treatment was knife excisions during 1960s-
216 1970s; laser conization during the 1980s; and since 1990s, large loop excision of the
217 transformational zone (LLETZ) (25). Different treatment modalities have been associated with
218 varying degrees of perinatal morbidity. More serious outcomes were noted for knife excisions
219 (aside from hysterectomy), followed by laser conization, and lastly LLETZ (30). Furthermore,
220 among LLETZ, smaller excisions were shown to reduce the risk of preterm birth, indicating that
221 adverse pregnancy outcomes may be minimized by preserving more healthy cervical tissue (12,
222 31).

223 However, the reproductive benefits gained through less aggressive treatment (preserving
224 more cervical tissue) may come at the cost of an increased risk of future invasive cervical cancer
225 (25, 32, 33). Incomplete excision of cervical precancer has been associated with
226 residual/recurrent CIN2/CIN3 (33). Given delays in childbirth and the wide adoption of cervical
227 cancer screening, more women and clinicians will face the dilemma where improper
228 management of CIN3 can increase the risk of cervical cancer on the one hand and complications
229 from overtreatment on the other. Therefore, to achieve an optimal balance between obstetric
230 safety and the risk of cancer, careful consideration should be made on an individual level. This is
231 one of the major challenges in the field, requiring proficiency not only in treatment but also in
232 management and colposcopy to identify the right women to treat.

233 Despite our large sample size and our sibling-comparison design, certain limitations of this
234 study should be noted. First, although CIN3 has always been treated in Sweden, we lack data on
235 actual treatment for CIN3. Also, there are no data on spontaneous abortion. Second,
236 misclassification of CIN2 as CIN3 is possible in the Swedish Cancer Register (especially after
237 2017), however, this misclassification would lead to a dilution of our results. Third, we were

238 unable to adjust for all possible confounders and include all potential outcomes (e.g.,
239 spontaneous abortion). Finally, whether our results can be generalized to low-income countries
240 remains unknown. However, we do not expect a weaker association in low-income countries,
241 given that we found a stronger association between CIN3 and adverse pregnancy outcomes
242 among women with a lower socioeconomic position.

243 In conclusion, women with treated CIN3 are more likely to experience preterm birth and
244 infection-related pregnancy outcomes, including chorioamnionitis and infant sepsis. These
245 results suggest that women treated for CIN3 should be recognized as “high-risk” and managed
246 accordingly, to reduce the risk of adverse pregnancy outcomes. However, treated women and
247 women facing treatment should also be informed that, over the last decades, the risk for adverse
248 pregnancy outcomes has decreased dramatically and modern treatment do not confer an
249 increased risk of perinatal death.

250

251 **Reproducible Research Statement:**

252 Protocol: not available.

253 Statistical Code: Available to interested readers by contacting Dr. Wei He at wei.he@ki.se.

254 Data: not available.

255 **Grant support:**

256 This work was supported by the Swedish Research Council [grant number: 2018-02547]; the

257 Swedish Cancer Society [grant number: 19 0266]; and FORTE [grant number: 2016-00081,

258 2018-00877]. Wei He is supported by Zhejiang University through “Hundred Talents Program”.

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- 347

348 **Figure legends**

349

350 **Figure 1.** Absolute rate of adverse pregnancy outcomes among women with a prior cervical
351 intraepithelial neoplasia grade 3 (CIN3) diagnosis, compared to the matched general population
352 of parous women in Sweden, by calendar year from 1973 to 2018. CIN3 was mainly treated with
353 knife excision during 1960s-1970s; laser conization in 1980s; and large loop excision of the
354 transformational zone (LLETZ) since the 1990s (following increased awareness of the perinatal
355 side effects of CIN3 treatment).

356 **Figure 2.** Odds ratios (ORs) and 95% confidence intervals (CIs) of adverse pregnancy outcomes
357 among women with a prior cervical intraepithelial neoplasia grade 3 (CIN3) diagnosis, compared
358 to the matched general Swedish population of parous women, by calendar year from 1973 to
359 2018. $P < 0.001$ for interaction between CIN3 diagnosis and year of delivery is noted for all
360 pregnancy outcomes, except for intrauterine fetal death (P for interaction=0.139). Women
361 diagnosed with CIN3 were mainly treated with knife excision during 1960s-1970s; laser
362 conization in the 1980s; and large loop excision of the transformational zone (LLETZ) since the
363 1990s (with increased awareness of the perinatal side effects of CIN3 treatment).

364 **Figure 3.** Odds ratios (ORs) and 95% confidence intervals (CIs) of adverse pregnancy outcomes
365 among women with a prior cervical intraepithelial neoplasia grade 3 (CIN3) diagnosis, compared
366 to the matched general Swedish population of parous women, from 2000 to 2018, by maternal
367 characteristics. Deliveries before 2000 were excluded to better reflect current clinical practice.
368 Small for gestational age and perinatal deaths were not statistically significantly different
369 between women who were and were not treated for CIN3 after 2000, thus these outcomes were
370 not included in the analyses. The p values for interaction were calculated by adding an

371 interaction term to the conditional logistic regression model (ordered categorical variables were
372 treated as continuous in the interaction analyses).

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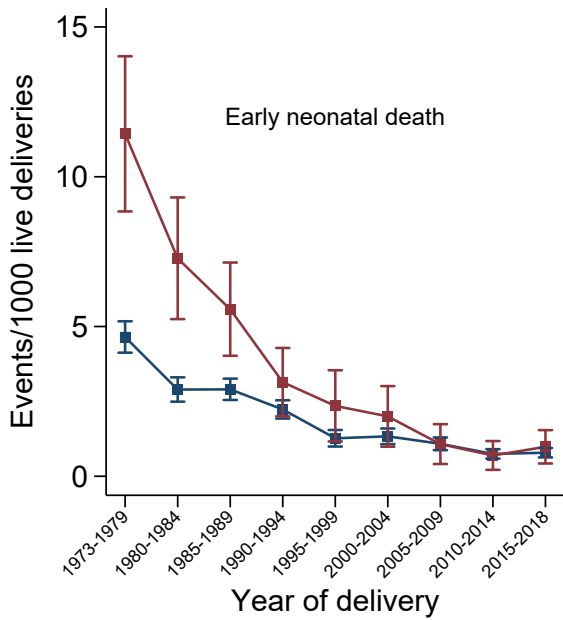
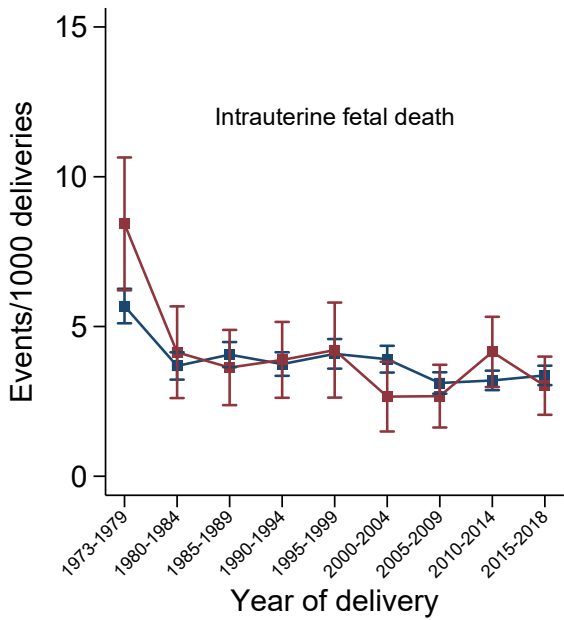
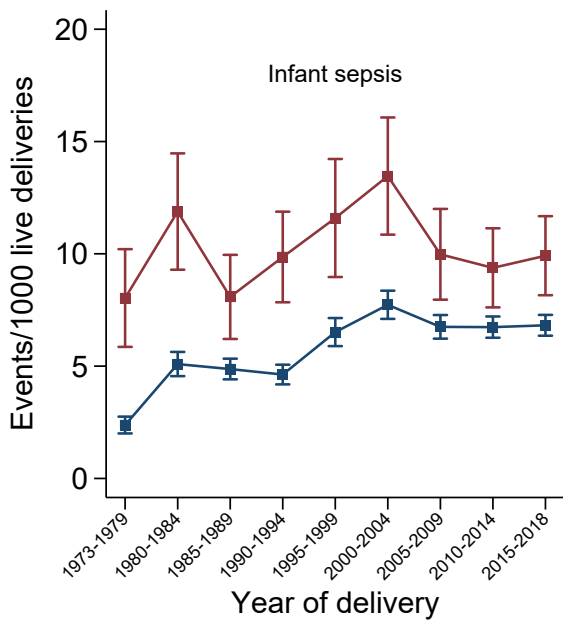
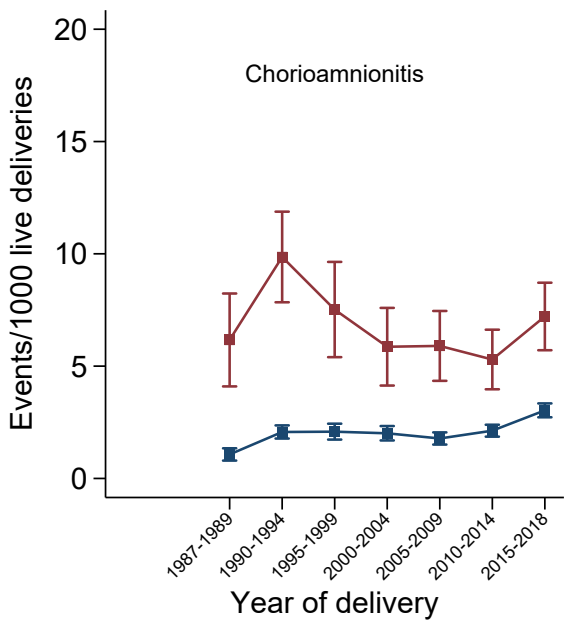
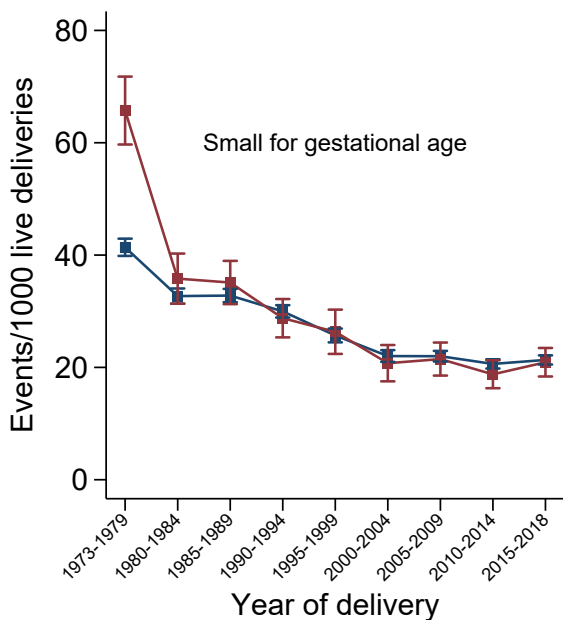
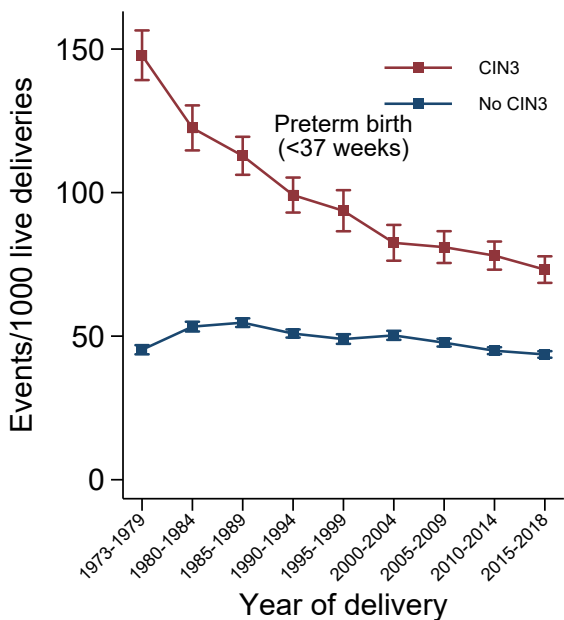
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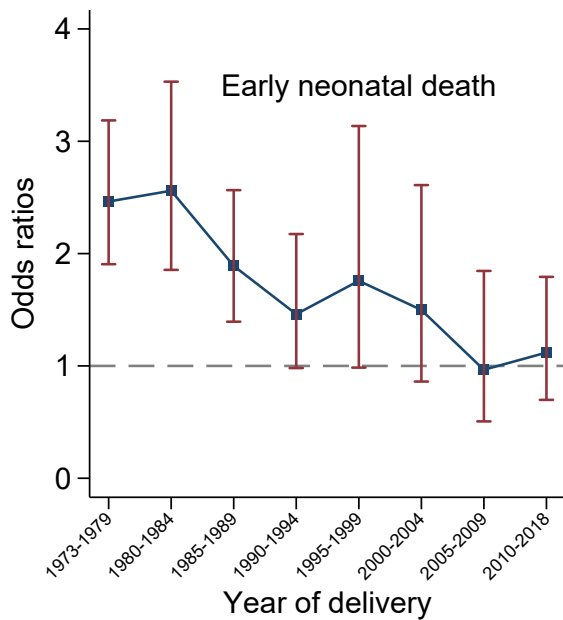
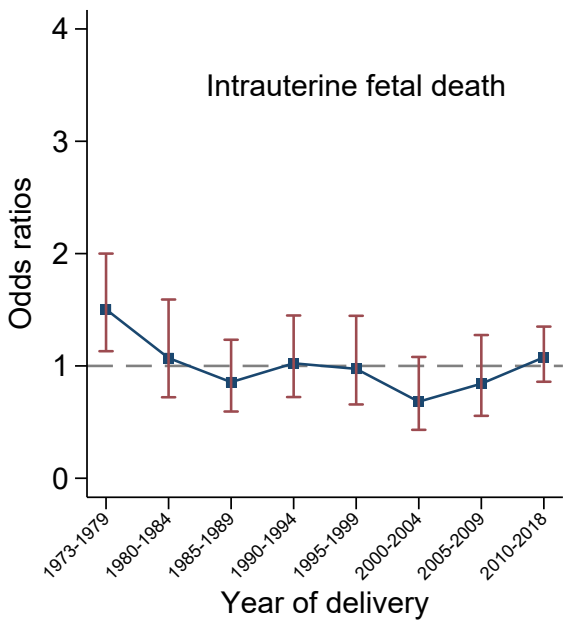
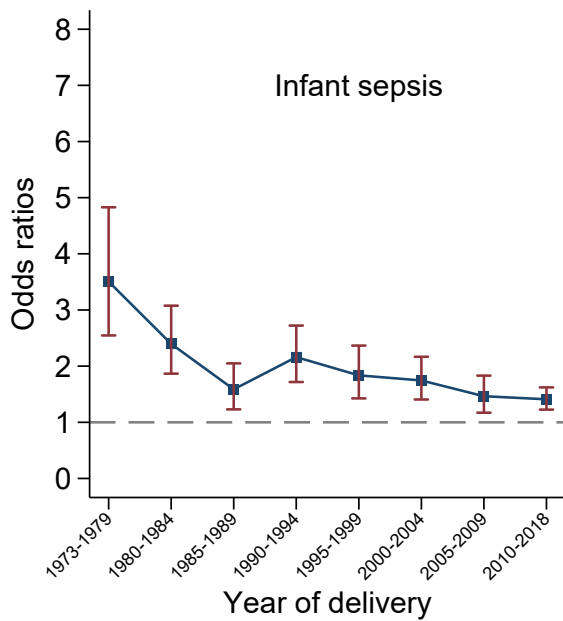
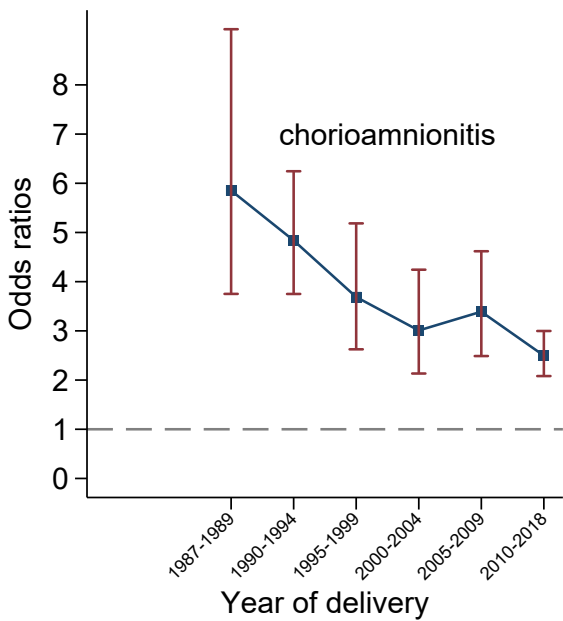
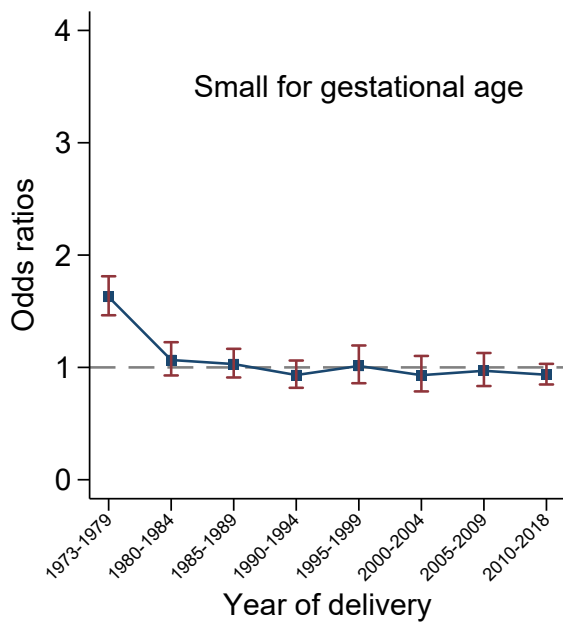
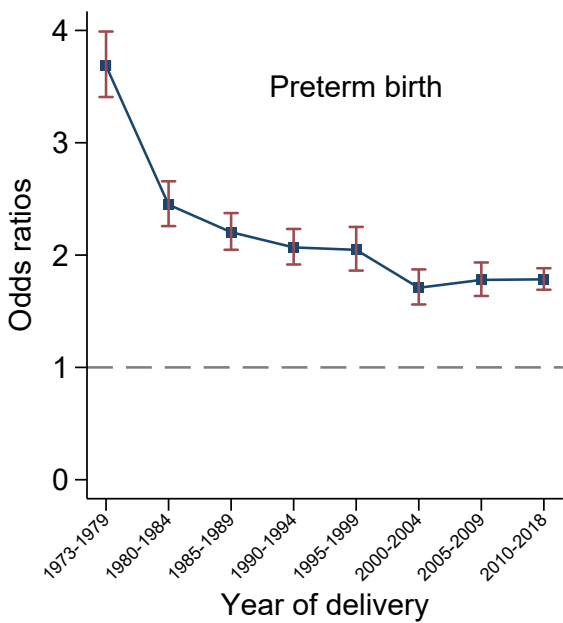
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Preterm birth
(<37 weeks)

Chorioamnionitis

Infant sepsis

Maternal age at delivery, yrs

$P_{\text{interaction}} < .001$

$P_{\text{interaction}} = .287$

$P_{\text{interaction}} = .074$

<25

25–29

30–34

≥ 35

Maternal years of education

$P_{\text{interaction}} = .014$

$P_{\text{interaction}} = .036$

$P_{\text{interaction}} = .023$

≤ 9

9–11

≥ 12

Maternal country of birth

$P_{\text{interaction}} = .064$

$P_{\text{interaction}} = .913$

$P_{\text{interaction}} = .882$

Swedish

Non-Swedish

Marital status

$P_{\text{interaction}} = .823$

$P_{\text{interaction}} = .217$

$P_{\text{interaction}} = .182$

Married

Unmarried

Parity

$P_{\text{interaction}} < .004$

$P_{\text{interaction}} < .001$

$P_{\text{interaction}} = .002$

1

2

3

≥ 4

Pre-pregnancy BMI

$P_{\text{interaction}} < .001$

$P_{\text{interaction}} = .136$

$P_{\text{interaction}} = .026$

<25

25–29

≥ 30

Smoking in early pregnancy

$P_{\text{interaction}} = .018$

$P_{\text{interaction}} = .656$

$P_{\text{interaction}} = .962$

No cigarette

1–9 cigarette

≥ 10 cigarette

0.50 1.0 2.0 4.0

0.50 1.0 2.0 4.0 6.0 8.0

0.50 1.0 2.0 4.0

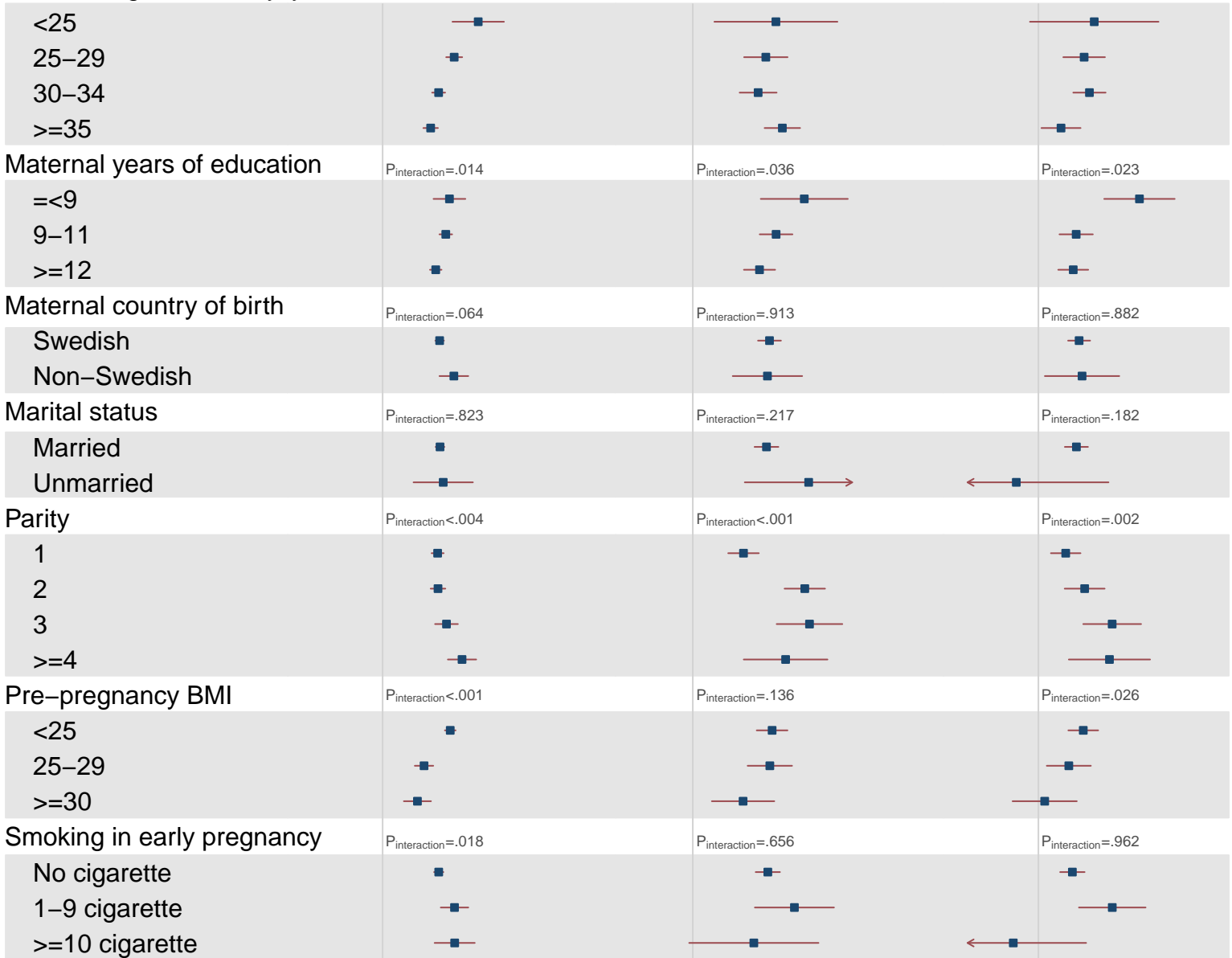


Table 1. Maternal characteristics to births occurring after a cervical intraepithelial neoplasia grade 3 (CIN3) diagnosis, compared to the matched general Swedish population of parous women and compared to their parous sisters, 1973-2018.

	General population comparison* (births N=862 950)		Sibling comparison (births N=51 334)	
	Matched Controls (N=784 500)	Diagnosed CIN3 (N= 78 450)	Controls (N=28 135)	Diagnosed CIN3 (N=23 199)
Calendar period of delivery				
1973-1979	65280(8.3)	6528(8.3)	2427(8.6)	1517(6.5)
1980-1989	155770(19.9)	15577(19.9)	5896(21.0)	4900(21.1)
1990-1999	156750(20.0)	15675(20.0)	6540(23.2)	5301(22.9)
2000-2009	168660(21.5)	16866(21.5)	6721(23.9)	5202(22.4)
2010-2018	238040(30.3)	23804(30.3)	6551(23.3)	6279(27.1)
Age at delivery, yrs				
≤24	33010(4.2)	3301(4.2)	1618(5.8)	1213(5.2)
25-29	211780(27.0)	21178(27.0)	8729(31.0)	7094(30.6)
30-34	319330(40.7)	31933(40.7)	11371(40.4)	9484(40.9)
≥35	220380(28.1)	22038(28.1)	6417(22.8)	5408(23.3)
Swedish healthcare region				
Stockholm-Gotland	160440(20.5)	16044(20.5)	5307(18.9)	4416(19.0)
Uppsala-örebro	130310(16.6)	13031(16.6)	4841(17.2)	3707(16.0)
Southeast	79980(10.2)	7998(10.2)	3114(11.1)	2478(10.7)
South	173590(22.1)	17359(22.1)	6026(21.4)	5201(22.4)
West	173420(22.1)	17342(22.1)	6308(22.4)	5351(23.1)
North	66760(8.5)	6676(8.5)	2522(9.0)	2046(8.8)
Education level, yrs				
≤9	77207(9.9)	8042(10.3)	2733(9.7)	2277(9.8)
10-12	339582(43.4)	34186(43.7)	11991(42.6)	10057(43.4)
>12	365763(46.7)	36023(46.0)	13393(47.6)	10858(46.8)
Missing	1948	199	18	7
Country of birth				
Sweden	722126(92.0)	73081(93.2)	27407(97.4)	22653(97.6)
Outside of Sweden	62374(8.0)	5369(6.8)	728(2.6)	546(2.4)
Preeclampsia				
No	767170(97.8)	76660(97.7)	27449(97.6)	22713(97.9)
Yes	17330(2.2)	1790(2.3)	686(2.4)	486(2.1)
Marital status				
Married	669205(93.7)	66531(93.5)	24268(94.2)	19870(94.0)
Unmarried	45013(6.3)	4654(6.5)	1497(5.8)	1260(6.0)
Missing	70282	7265	2370	2069
Parity				
1	265865(33.9)	26297(33.5)	9083(32.3)	7840(33.8)
2	302865(38.6)	30072(38.3)	11064(39.3)	9025(38.9)
3	145867(18.6)	14863(18.9)	5531(19.7)	4367(18.8)
≥4	69903(8.9)	7218(9.2)	2457(8.7)	1967(8.5)
Pre-pregnancy BMI[†]				
<25 kg/m ²	516814(79.8)	50538(78.2)	19209(82.7)	15182(77.9)
25-29 kg/m ²	79283(12.2)	8487(13.1)	2530(10.9)	2642(13.6)
≥30 kg/m ²	51242(7.9)	5571(8.6)	1480(6.4)	1673(8.6)
Missing	46491	4787	1588	1464

Smoking in early pregnancy[†]				
Non smoker	394136(70.2)	38846(69.6)	13629(68.7)	11932(71.6)
1-9 cigarettes/day	123836(22.0)	12535(22.5)	4392(22.1)	3545(21.3)
≥10 cigarettes/day	43672(7.8)	4447(8.0)	1821(9.2)	1178(7.1)
Missing	132186	13555	4965	4306

Abbreviation: BMI, body mass index.

* Optimal 1:10 pair match with exact matching for calendar period of delivery, age at delivery, and Swedish healthcare region.

[†] Data available only after 1982.

Table 2. Adverse pregnancy outcomes among women with a prior cervical intraepithelial neoplasia grade 3 (CIN3) diagnosis, compared to the matched general Swedish population of parous women and compared to their parous sisters, 1973-2018.

	General population comparison*				Sibling comparison*			
	No. of events (events/1000 births)		Absolute rate difference/1000 live births (95% CI)	Odds ratio [†] (95% CI)	No. of events (events/1000 deliveries)		Absolute rate difference/1000 live births (95% CI)	Odds ratio [‡] (95% CI)
	Controls (N=784 500)	Diagnosed CIN3 (N= 78 450)	Controls (N=28 135)		Diagnosed CIN3 (N=23 199)			
Preterm birth								
Overall	37876 (48.5)	7452 (95.4)	46.89 (44.67-49.11)	2.09 (2.03-2.15)	1322 (47.2)	2183 (94.5)	47.30 (42.59-52.01)	2.27 (2.08-2.49)
By Gestational Age								
32-37 weeks	32756 (41.9)	6017 (77.0)	35.08 (33.08-37.08)	1.94 (1.88-2.00)	1149 (41.0)	1791 (77.5)	36.51 (32.21-40.81)	2.11 (1.92-2.32)
28-32 weeks	3497 (4.5)	972 (12.4)	7.96 (7.17-8.76)	2.98 (2.76-3.21)	120 (4.3)	268 (11.6)	7.32 (5.73-8.90)	4.21 (3.11-5.69)
22-28 weeks	1623 (2.1)	463 (5.9)	3.85 (3.30-4.40)	3.00 (2.69-3.34)	53 (1.9)	124 (5.4)	3.48 (2.40-4.55)	3.08 (1.95-4.85)
By Labor Onset [§]								
Spontaneous preterm birth	7418 (13.2)	836 (14.9)	1.70 (0.65-2.76)	2.12 (2.05-2.20)	215 (12.2)	222 (14.6)	2.42 (-0.10-4.93)	2.25 (1.97-2.57)
Iatrogenic preterm birth	17884 (31.9)	3635 (65.0)	33.06 (30.89-35.22)	1.15 (1.06-1.24)	553 (31.3)	1023 (67.2)	35.89 (31.02-40.76)	1.46 (1.11-1.93)
Small for gestational age	20797 (26.7)	2230 (28.6)	1.93 (0.69-3.18)	1.06 (1.01-1.11)	707 (25.3)	624 (27.1)	1.78 (-1.05-4.60)	1.08 (0.94-1.23)
Infection-related outcomes								
Chorioamnionitis	1315 (2.1)	421 (6.8)	4.69 (4.03-5.36)	3.23 (2.89-3.62)	41 (1.9)	119 (6.4)	4.53 (3.25-5.82)	3.68 (2.21-6.12)
Infant sepsis	4585 (5.9)	791 (10.1)	4.26 (3.53-4.98)	1.72 (1.60-1.86)	151 (5.4)	229 (9.9)	4.52 (2.98-6.07)	2.03 (1.59-2.59)
Perinatal death								
Intrauterine fetal death	2954 (3.8)	308 (3.9)	0.16 (-0.30-0.62)	1.02 (0.90-1.14)	98 (3.5)	82 (3.5)	0.05 (-0.98-1.08)	0.97 (0.70-1.35)
Early neonatal death	1421 (1.8)	261 (3.3)	1.52 (1.11-1.94)	1.83 (1.61-2.09)	51 (1.8)	70 (3.0)	1.21 (0.34-2.08)	1.80 (1.17-2.75)

* Stillbirths were excluded in all analyses, except for the analyses of intrauterine death. Women with missing information on each investigated pregnancy outcome were excluded in the corresponding analyses.

† Analysis among matched pairs (exact matched for calendar period of delivery, age at delivery and Swedish healthcare region) and adjusted for years of education, country of birth, preeclampsia diagnosis, marital status, parity, pre-pregnancy body mass index, and smoking in early pregnancy.

‡ Analysis among sibling pairs and adjusted for calendar period of delivery, age at delivery, Swedish healthcare region, years of education, country of birth, preeclampsia diagnosis, marital status, parity, smoking in early pregnancy, and pre-pregnancy body mass index.

§ Information on labor onset (spontaneous or iatrogenic) was available from 1990 in the Swedish Medical Birth Register.

|| Information on chorioamnionitis was available from 1987 (this diagnosis does not exist in ICD8).