2023-11-27

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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

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

Wei He[1,2,3*], Ph.D., Pär Sparen[3], Ph.D., Fang Fang[4], M.D, Ph.D., Verena Sengpiel[5,6], M.D., Ph.D., Björn Strander [6,7], M.D., Ph.D., Kamila Czene[3], Ph.D.

[1] Chronic Disease Research Institute, the Children's Hospital, and National Clinical Research Center for Child Health, School of Public Health, School of Medicine, Zhejiang University, Hangzhou, Zhejiang, China

[2] Department of Nutrition and Food Hygiene, School of Public Health, Zhejiang University, Hangzhou, Zhejiang, China

[3] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

[4] Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

[5] Region Västra Götaland, Department of Obstetrics and Gynecology, Sahlgrenska University Hospital, Gothenburg, Sweden

[6] Department of Obstetrics and Gynecology, Sahlgrenska Academy, University of Gothenburg, Sweden

[7] Regional Cancer Center West, Gothenburg, Sweden

[*] **Corresponding author:**

Dr. Wei He

Chronic Disease Research Institute, the Children's Hospital, and National Clinical Research Center for Child Health, School of Public Health, School of Medicine, Zhejiang University, 866 Yu-hang-tang Road, Hangzhou, Zhejiang, 310058 China

Tel: (86) 571-8820-8125

E-mail: wei.he@ki.se

Abstract

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

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

Design: Population- and sibling-matched cohort study.

Setting: Sweden, 1973-2018.

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

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

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

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

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

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

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

Introduction

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

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

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

Methods

Data sources

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

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

Study population

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

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

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

CIN3

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

Preterm birth and related outcomes

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

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

Covariates

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

Statistical analysis

Conditional logistic regression with robust standard errors (Stata's clogit command) was used in the matched general population comparison analyses to investigate the association between ever having a CIN3 diagnosis and pregnancy outcomes. The analyses were conducted 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. Conditional logistic regression was also used in the sibling comparison analyses to adjust for common factors shared between sisters.

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

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

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

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

Role of the Funding source

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

Results

Population characteristics

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

Pregnancy outcomes among women diagnosed with CIN3

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

Pregnancy outcomes among women diagnosed with CIN3, by calendar year

Figure 1 shows the absolute rate of adverse pregnancy outcomes by CIN3 over time. Compared to the matched general population, women with a prior CIN3 diagnosis were generally more likely to have an adverse pregnancy outcome. However, over time this risk difference attenuated. From 1973-1979 to 2010-2018, the OR (95% CI) decreased from 3.69 (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 (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

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

Pregnancy outcomes among women diagnosed with CIN3, by maternal characteristics

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

Discussion

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

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

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

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

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

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

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

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

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

Reproducible Research Statement:

Protocol: not available.

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

Data: not available.

Grant support:

This work was supported by the Swedish Research Council [grant number: 2018-02547]; the Swedish Cancer Society [grant number: 19 0266]; and FORTE [grant number: 2016-00081, 2018-00877]. Wei He is supported by Zhejiang University through “Hundred Talents Program”.

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Figure legends

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

Figure 2. Odds ratios (ORs) and 95% confidence intervals (CIs) of 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, by calendar year from 1973 to 2018. $P < 0.001$ for interaction between CIN3 diagnosis and year of delivery is noted for all pregnancy outcomes, except for intrauterine fetal death (P for interaction=0.139). Women diagnosed with CIN3 were mainly treated with knife excision during 1960s-1970s; laser conization in the1980s; and large loop excision of the transformational zone (LLETZ) since the 1990s (with increased awareness of the perinatal side effects of CIN3 treatment).

Figure 3. Odds ratios (ORs) and 95% confidence intervals (CIs) of 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, from 2000 to2018, by maternal characteristics. Deliveries before 2000 were excluded to better reflect current clinical practice. Small for gestational age and perinatal deaths were not statistically significantly different between women who were and were not treated for CIN3 after 2000, thus these outcomes were 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).

Current author address:

Wei He: Chronic Disease Research Institute, the Children's Hospital, and National Clinical Research Center for Child Health, School of Public Health, School of Medicine,
Zhejiang University,
866 Yu-hang-tang Road, Hangzhou, Zhejiang, 310058 China

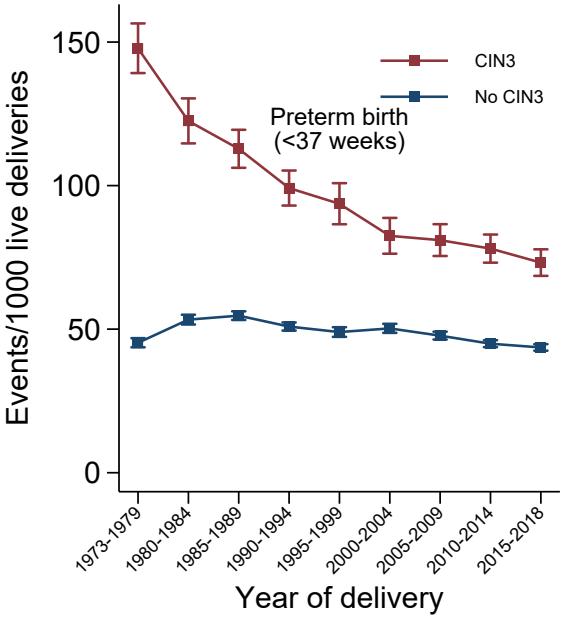
Pär Sparen: Department of Medical Epidemiology and Biostatistics,
Karolinska Institutet,
Nobels väg 12 A, Stockholm, 171 77 Sweden

Fang Fang: Institute of Environmental Medicine,
Karolinska Institutet,
Nobels väg 13, Stockholm, 171 65 Sweden

Verena Sengpiel: Department of Obstetrics and Gynecology, Sahlgrenska University of Hospital / Östra,
Journalvägen 6, Göteborg, 41 685 Sweden

Björn Strander: Regionalt Cancercentrum Väst,
Medicinaregatan 18G, Sahlgrenska Universitetssjukhuset, 413 45 Göteborg, Sweden

Kamila Czene: Department of Medical Epidemiology and Biostatistics,
Karolinska Institutet,
Nobels väg 12 A, Stockholm, 171 77 Sweden


Preterm birth
(<37 weeks)
CIN3
No CIN3
Events/1000 live deliveries
0
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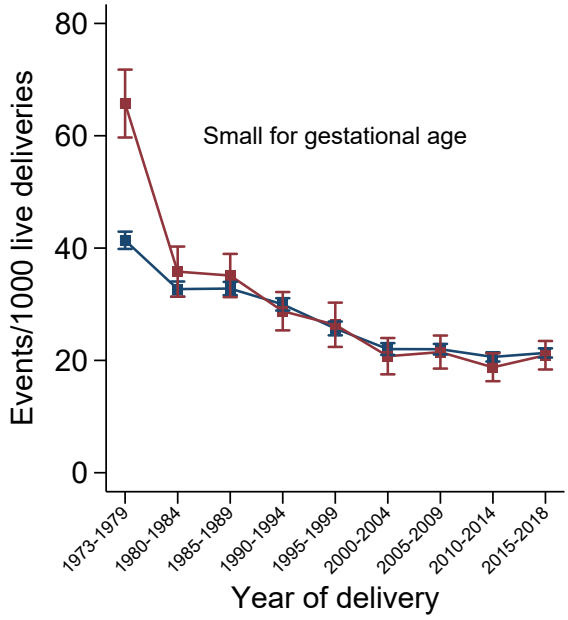
100
150
1973-1979
1980-1984
1985-1989
1990-1994
1995-1999
2000-2004
2005-2009
2010-2014
2015-2018
Year of delivery


Small for gestational age
Events/1000 live deliveries
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60
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1973-1979
1980-1984
1985-1989
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2000-2004
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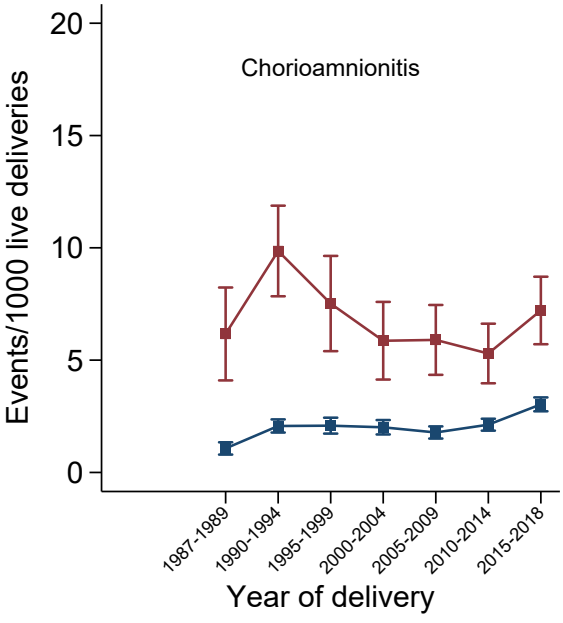
2010-2014
2015-2018
Year of delivery


Chorioamnionitis
Events/1000 live deliveries
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1987-1989
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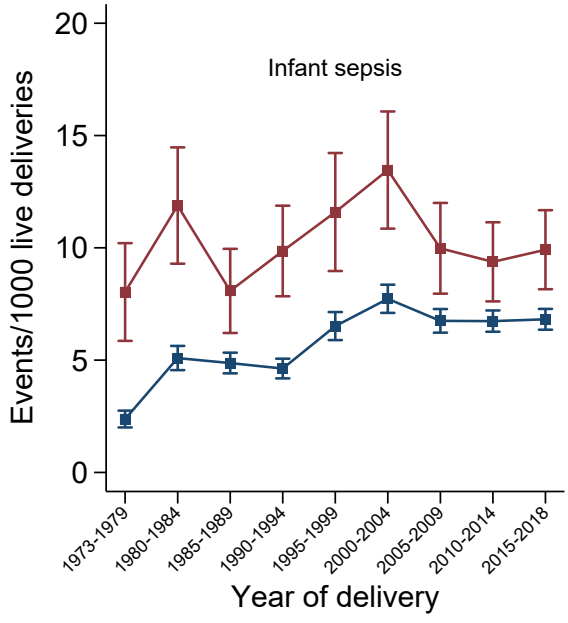
2005-2009
2010-2014
2015-2018
Year of delivery


Infant sepsis
Events/1000 live deliveries
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1973-1979
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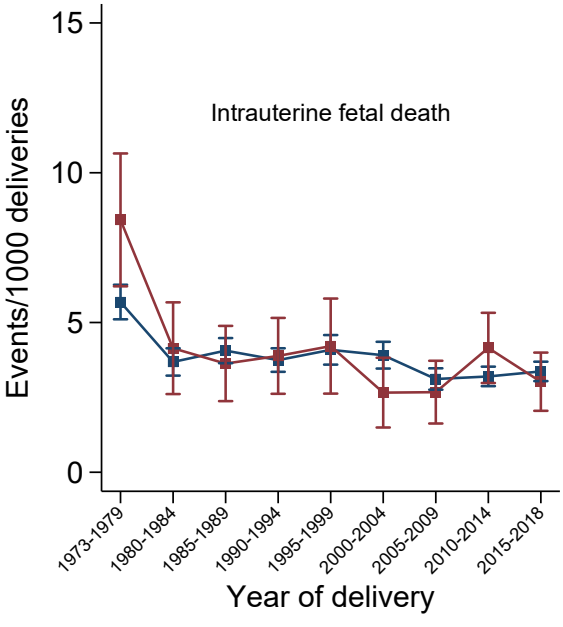
2015-2018
Year of delivery


Intrauterine fetal death
Events/1000 deliveries
0
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10
15
1973-1979
1980-1984
1985-1989
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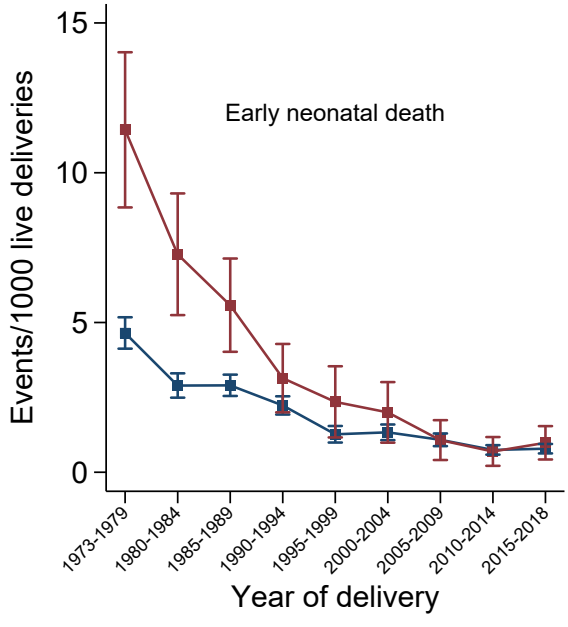
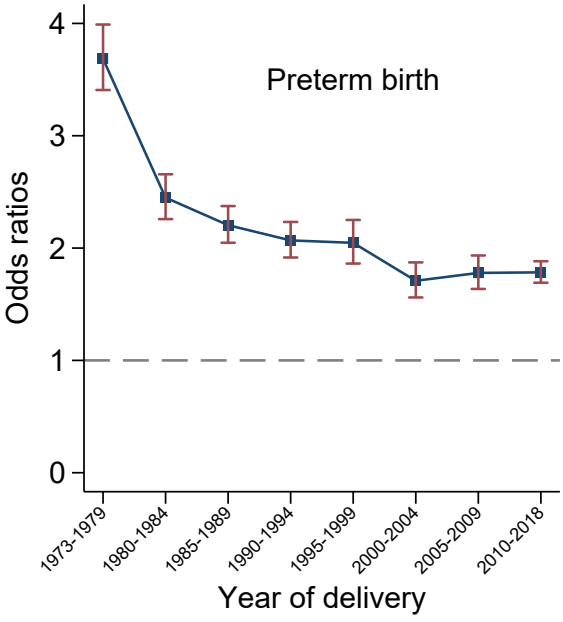
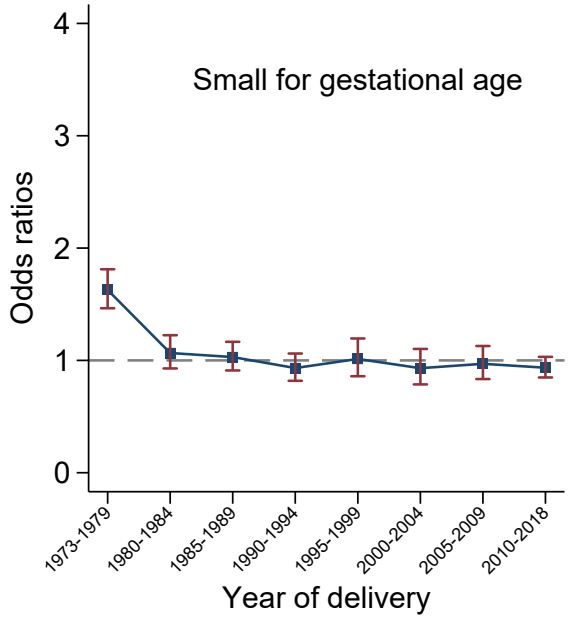
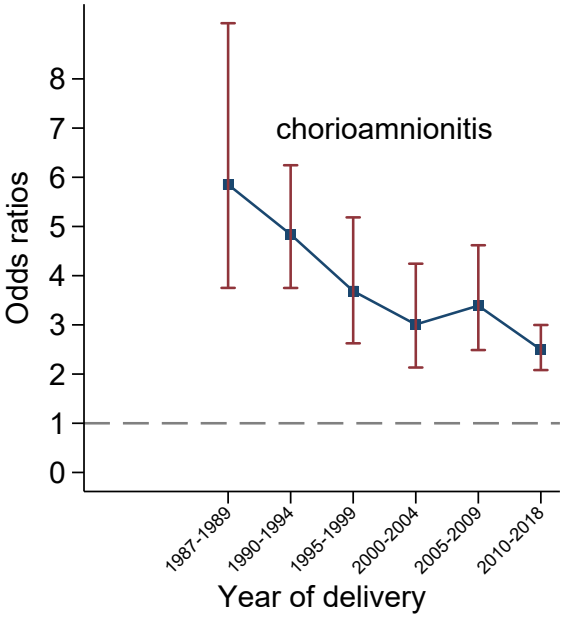
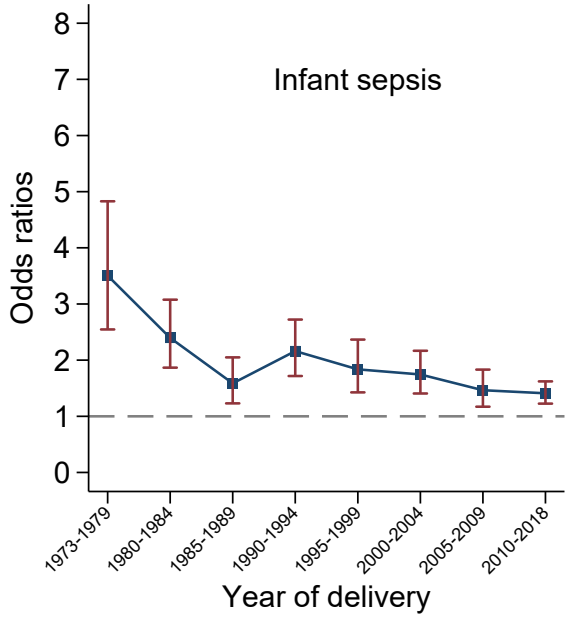
1995-1999
2000-2004
2005-2009
2010-2014
2015-2018
Year of delivery

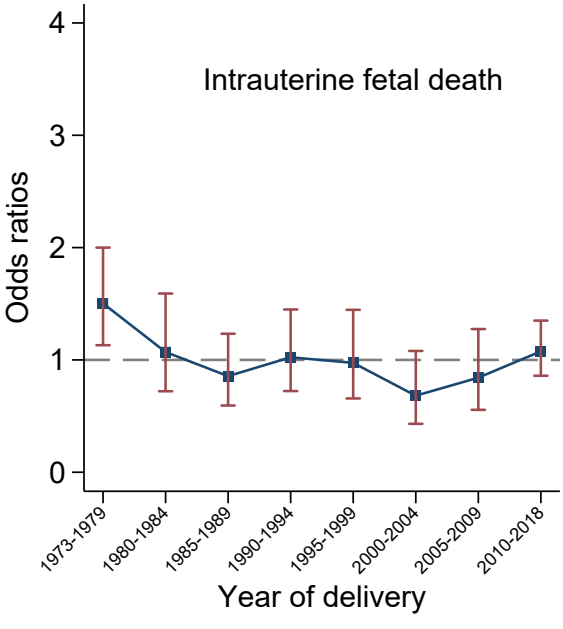

Early neonatal death
Events/1000 live deliveries
0
5
10
15
1973-1979
1980-1984
1985-1989
1990-1994
1995-1999
2000-2004
2005-2009
2010-2014
2015-2018
Year of delivery

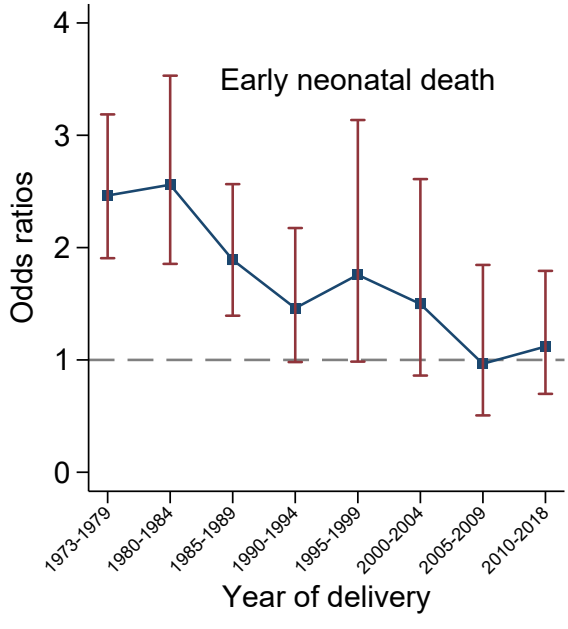

Preterm birth
Odds ratios
0
1
2
3
4
1973-1979
1980-1984
1985-1989
1990-1994
1995-1999
2000-2004
2005-2009
2010-2018
Year of delivery


Small for gestational age
Odds ratios
0
1
2
3
4
1973-1979
1980-1984
1985-1989
1990-1994
1995-1999
2000-2004
2005-2009
2010-2018
Year of delivery


chorioamnionitis
Odds ratios
0
1
2
3
4
5
6
7
8
1987-1989
1990-1994
1995-1999
2000-2004
2005-2009
2010-2018
Year of delivery


Infant sepsis
Odds ratios
0
1
2
3
4
5
6
7
8
1973-1979
1980-1984
1985-1989
1990-1994
1995-1999
2000-2004
2005-2009
2010-2018
Year of delivery


Intrauterine fetal death
Odds ratios
0
1
2
3
4
1973-1979
1980-1984
1985-1989
1990-1994
1995-1999
2000-2004
2005-2009
2010-2018
Year of delivery


Early neonatal death
Odds ratios
0
1
2
3
4
1973-1979
1980-1984
1985-1989
1990-1994
1995-1999
2000-2004
2005-2009
2010-2018
Year of delivery

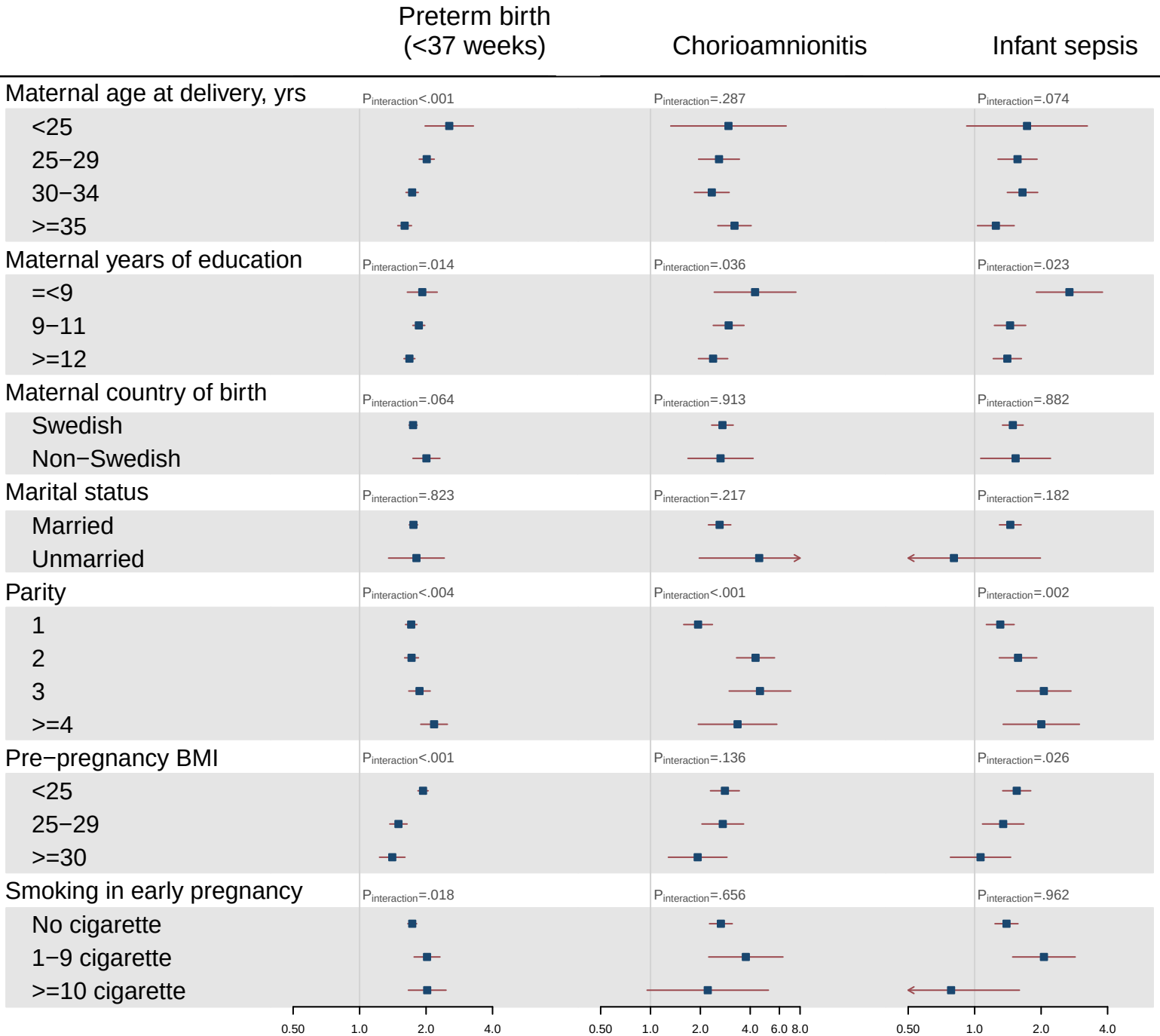

Preterm birth (<37 weeks)
Chorioamnionitis
Infant sepsis
Maternal age at delivery, yrs
Pinteraction<.001
Pinteraction=.287
Pinteraction=.074
<25
25−29
30−34
>=35
Maternal years of education
Pinteraction=.014
Pinteraction=.036
Pinteraction=.023
=<9
9−11
>=12
Maternal country of birth
Pinteraction=.064
Pinteraction=.913
Pinteraction=.882
Swedish
Non−Swedish
Marital status
Pinteraction=.823
Pinteraction=.217
Pinteraction=.182
Married
Unmarried
Parity
Pinteraction<.004
Pinteraction<.001
Pinteraction=.002
1
2
3
>=4
Pre−pregnancy BMI
Pinteraction<.001
Pinteraction=.136
Pinteraction=.026
<25
25−29
>=30
Smoking in early pregnancy
Pinteraction=.018
Pinteraction=.656
Pinteraction=.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)		No. of events (events/1000 deliveries)		Absolute rate difference/1000 live births (95% CI)	
	Controls (N=784 500)	Diagnosed CIN3 (N= 78 450)		Odds ratio† (95% CI)	Controls (N=28 135)	Diagnosed CIN3 (N=23 199)		Odds ratio‡ (95% CI)
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 neontal 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).