



Quadrivalent human papillomavirus vaccination before pregnancy and pregnancy outcomes: nationwide, population based case-control study

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ABSTRACT

OBJECTIVE

To evaluate the association between quadrivalent human papillomavirus vaccination before pregnancy and subsequent risk of adverse pregnancy outcomes.

DESIGN

Nationwide, population based matched case-control study.

SETTING

Population of Sweden, from 1 January 2006 to 31 December 2023.

PARTICIPANTS

624 713 singleton births among nulliparous women aged 16-35 years in Sweden between 2006 and 2023; 92 620 (14.8%) women had received quadrivalent human papillomavirus vaccination before pregnancy.

MAIN OUTCOME MEASURES

Risk of adverse pregnancy outcomes associated with quadrivalent human papillomavirus vaccination, with preterm birth (<37 weeks), including its subtypes, and spontaneous preterm birth as primary outcomes and preterm prelabour rupture of membranes, prelabour rupture of membranes, small for gestational age infant (<10th centile), severe small for gestational age infant (<3rd centile), stillbirth, and neonatal mortality as secondary outcomes. Effect modification by age at human papillomavirus vaccination was assessed. Conditional logistic regression was used to estimate odds ratios and adjusted odds ratios with 95% confidence intervals (CIs).

RESULTS

After adjustment for confounders, quadrivalent human papillomavirus vaccination was associated with lower odds of all included adverse pregnancy outcomes. Statistically significant associations were observed for preterm birth (<37 weeks) (adjusted odds ratio 0.95, 95% CI 0.91 to 0.99), very preterm birth (28 weeks to 31 weeks) (0.85, 0.75 to 0.97), spontaneous preterm birth (0.95, 0.91 to 0.99), preterm prelabour rupture of membranes (0.93, 0.87 to 1.00), and severe small for gestational age infant (0.92, 0.87 to 0.97). Risk reduction was generally more pronounced among women vaccinated at younger ages.

CONCLUSIONS

Quadrivalent human papillomavirus vaccination before pregnancy was associated with a lower risk of adverse pregnancy outcomes, particularly among women vaccinated at earlier ages, extending benefits of human papillomavirus vaccination beyond cancer prevention.

Introduction

Preterm birth is one of the leading global causes of newborn mortality and a major contributor to medical and social impairments in adulthood,^{1 2} but effective treatment options and preventive measures remain limited. Persistent infections with high risk human papillomavirus are the primary cause of cervical precancer and cancer.³ Beyond persistent high risk human papillomavirus infection, cervical precancer and cervical cancer risk may also be influenced by systemic immunosuppression, vaginal dysbiosis, smoking, number of sexual partners, and young age at first pregnancy.⁴ Emerging evidence suggests that human papillomavirus infection is associated with an increased risk of adverse pregnancy outcomes, including preterm birth.⁵⁻⁹ Excisional treatments of the cervix, commonly performed for high grade cervical lesions and early stage cervical cancer caused by human papillomavirus,¹⁰ have also been shown to increase the risk of adverse pregnancy outcomes.^{9 11} Because these lesions and treatments often occur during reproductive age, human papillomavirus infection may be an important and potentially preventable contributor to preterm birth.

In Sweden, the first human papillomavirus vaccine became available in 2006.¹² From 2007 subsidised human papillomavirus vaccination was offered to girls aged 13-17 years, and in 2012 a free school based programme for girls aged 10-12 years was introduced alongside catch-up vaccination for girls born in 1993-98.^{12 13} Since 2020 gender neutral human

WHAT IS ALREADY KNOWN ON THIS TOPIC

Preterm birth is a leading global cause of neonatal mortality and is associated with long term morbidity and substantially higher healthcare costs

Human papillomavirus (HPV) infection and treatment of cervical lesions are associated with an increased risk of adverse pregnancy outcomes

Existing studies suggest HPV vaccination may reduce adverse pregnancy outcomes but are limited by the lack of nationwide linked data and detailed confounder control

WHAT THIS STUDY ADDS

In this nationwide Swedish register based study, quadrivalent HPV vaccination before pregnancy was associated with a reduced risk of adverse pregnancy outcomes, especially preterm related outcomes

The observed reduction in risk was generally greater among women vaccinated at younger ages

The findings suggest that the benefits of HPV vaccination may extend beyond cancer prevention to the prevention of adverse pregnancy outcomes, with broader implications for maternal and child public health

papillomavirus vaccination has been offered through the school based programme.¹³ Human papillomavirus vaccination offers highly effective protection against human papillomavirus infection, precancer, and cancers,¹⁴⁻¹⁷ with more pronounced protection observed among individuals receiving the vaccines at younger ages.¹⁶ With sustained protection,^{16 17} we expect human papillomavirus vaccination to have a beneficial impact on pregnancy outcomes.^{18 19} Given that a large share of human papillomavirus vaccine doses worldwide are delivered to girls of school age through routine vaccination programmes, even modest reproductive benefits could translate into substantial population level health gains and further strengthen the clinical and public health value of human papillomavirus vaccination.

Data from Denmark, Australia, Finland, and Scotland suggest that human papillomavirus vaccination before pregnancy may be associated with a reduced risk of some adverse pregnancy outcomes.¹⁹⁻²³ However, previous studies have often lacked nationwide, large scale data with individual level linkage, which limits detailed confounder control and increases the potential for residual confounding, and have frequently examined individual pregnancy outcomes in isolation. In this study, we aimed to evaluate the association between quadrivalent human papillomavirus (qHPV) vaccination and risk of adverse pregnancy outcomes by using population based nationwide, high quality Swedish registers.

Methods

Study population and study design

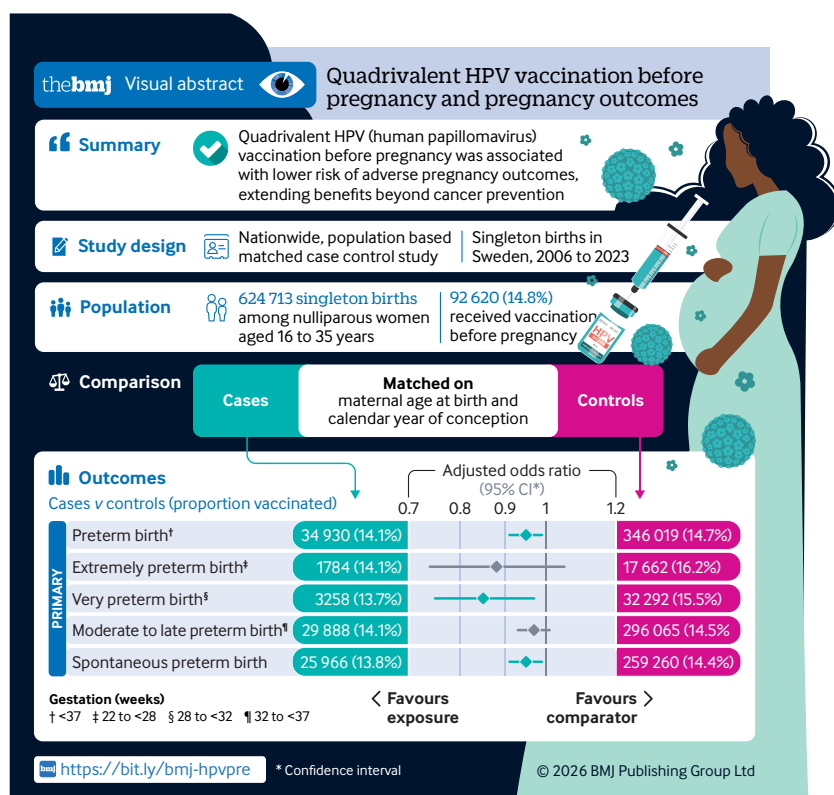
Our study population included all singleton births (gestational age ≥ 22 weeks) among nulliparous women aged 16 to 35 years between 1 January 2006 and 31 December 2023. We excluded births from women who immigrated to Sweden after 9 years of age during the study period, women whose first recorded human papillomavirus vaccination before childbirth was the bivalent or nonavalent human papillomavirus vaccine, women with missing information on the length of pregnancy, and women vaccinated after conception (fig 1). This study used data from several Swedish nationwide registers, with individual level information linked across registers through the unique personal identification number assigned to all residents living at least one year in Sweden.^{24 25}

For each pregnancy outcome, we did a matched case-control analysis (fig 1) to reduce strong confounding by matching factors. We defined cases as women experiencing the outcome of interest, including preterm birth, spontaneous preterm birth (sPTB), preterm prelabour rupture of membranes (pPROM), prelabour rupture of membranes (PROM) at term, small for gestational age (SGA) infant (<10 th centile), severe SGA infant (<3 rd centile), stillbirth, and neonatal mortality. Preterm birth and sPTB were the primary outcomes. We selected controls from women without the specific outcome. Cases and controls were exactly matched on maternal age at birth and calendar year of conception, with up to 10 controls per case. The matching procedure is detailed in the supplementary materials.

We selected a matched case-control design as the primary analytical approach because human papillomavirus vaccination status differed markedly by maternal age and calendar year, two strong and correlated factors in this setting. We therefore implemented exact matching on maternal age at birth and calendar year of conception at the design stage to improve comparability between vaccinated and unvaccinated women within strata defined by these factors. This approach allowed comparison within specific combinations of maternal age and calendar year, whereas a conventional cohort analysis would typically rely on model based adjustment for these variables.

Exposure

The exposure was qHPV vaccination before pregnancy, defined as receipt of at least one dose of qHPV vaccine before conception. We obtained the qHPV vaccination records from multiple registers, including the Swedish HPV Vaccination Register (SVEVAC),²⁶ the Prescribed Drug Register (PDR),²⁷ and the National Vaccination Register (NVR).²⁸ SVEVAC was a voluntary register of human papillomavirus vaccinations administered during 2006-15,²⁶ whereas the NVR has provided virtually complete documentation of vaccinations delivered within the national vaccination programme



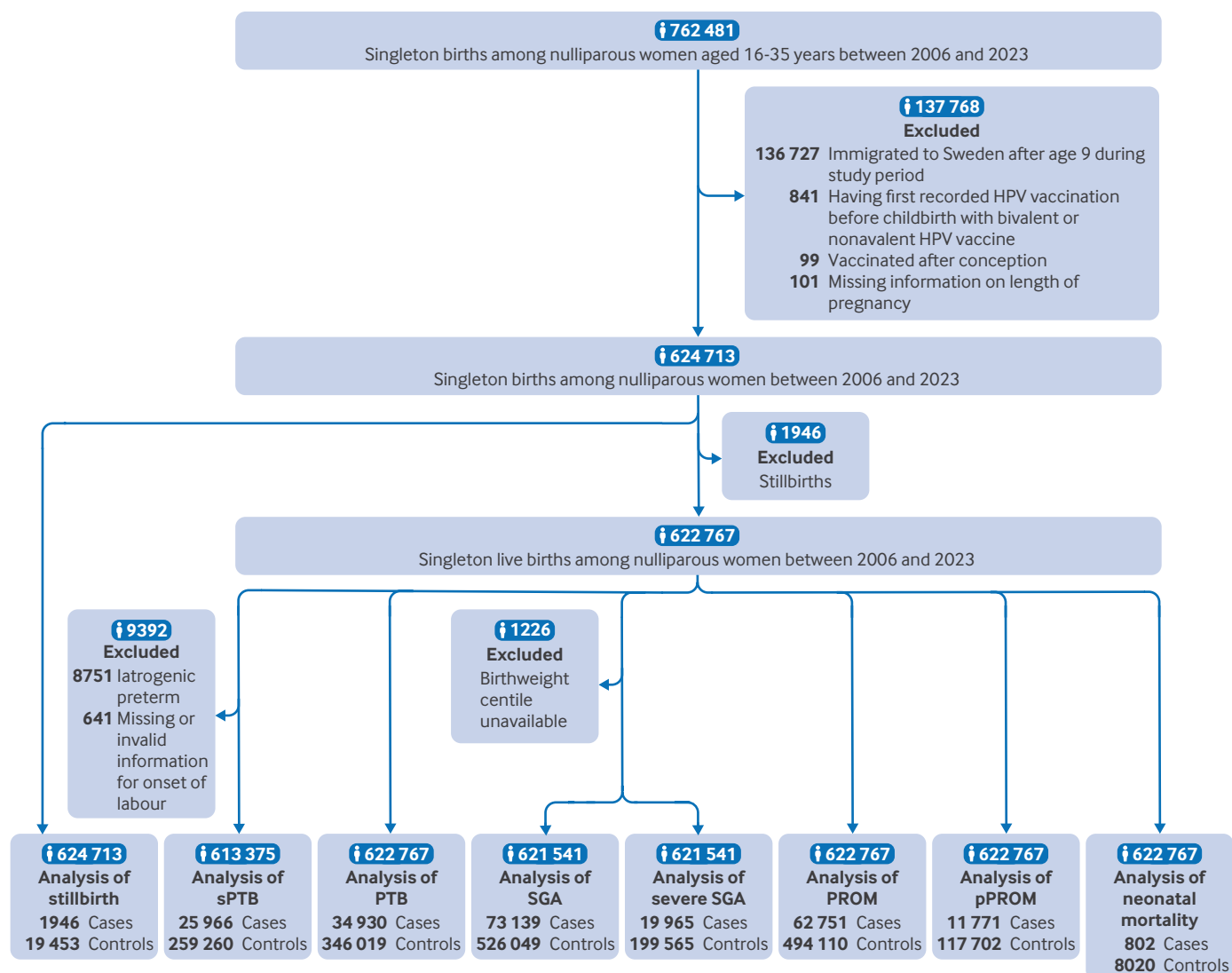


Fig 1 | Flow chart of study population. HPV=human papillomavirus; pPROM=preterm prelabour rupture of membranes; PROM=prelabour rupture of membranes at 37+ weeks; PTB=preterm birth; SGA=small for gestational age; sPTB=spontaneous preterm birth

since 2013.²⁸ The PDR has recorded all dispensed prescription drugs since 2005, including subsidised human papillomavirus vaccines provided outside the organised programme.²⁷ In our study, we used SVEVAC and NVR as the primary data sources, supplemented by records from the PDR.

Outcomes

We obtained information on adverse pregnancy outcomes from the Medical Birth Register (MBR).²⁹ The primary outcomes were preterm birth and sPTB. We defined preterm birth as birth before 37 completed weeks of gestation and analysed it as a binary variable. We further classified preterm birth by gestational age at birth according to the World Health Organization's definition as extremely preterm birth (22-<28 weeks), very preterm birth (28-<32 weeks), and moderate to late preterm birth (32-<37 weeks).³⁰ We defined

sPTB as preterm birth following pPROM or preterm labour, excluding deliveries initiated by induction of labour or caesarean section. Secondary outcomes were pPROM, PROM at term, SGA infant, severe SGA infant, stillbirth, and neonatal mortality. We defined pPROM by using ICD-10 (international classification of diseases, 10th revision) code O42 and delivery before 37 completed weeks of gestation. We defined PROM at term by using ICD-10 code O42 with delivery at 37 or more completed weeks of gestation or ICD-10 codes O756A, O756B, or O756X. We defined SGA and severe SGA infants as birth weight below the 10th and 3rd centiles, respectively, for gestational age and sex according to the ultrasonography based Swedish reference curve of estimated fetal growth.³¹ We defined stillbirth as fetal loss after 22 completed weeks of gestation and neonatal mortality as death within the first 27 completed days of life. We have also provided

detailed definitions, diagnostic codes, and timing of all outcomes in supplementary table S1. The outcomes were prespecified in a statistical analysis plan provided in the supplementary materials.

Covariates

As potential confounders, we considered calendar year of conception, maternal age at birth, self-reported cigarette smoking at the first prenatal visit, body mass index at the first prenatal visit, assisted reproduction, and maternal diagnoses from the MBR (supplementary table S2); women's county of residence and their mothers' country of birth, from the Total Population Register (TPR);²⁵ and annual household income level and highest educational level from the Swedish Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA).³² We identified biological and adoptive mothers for each woman through the Multi-Generation Register.³³ Data on high grade cervical lesions, defined as cervical intraepithelial neoplasia grades 2 or worse, adenocarcinoma in situ or worse, or invasive cervical cancers, came from the Swedish National Cervical Screening Registry (NKCx).³⁴ We have also provided detailed definitions and timing of all covariates in supplementary table S1.

Statistical analyses

The primary analytical approach was prespecified in a statistical analysis plan provided in the supplementary materials. We used descriptive statistics to summarise characteristics of the study population by human papillomavirus vaccination status before pregnancy and present them as counts and percentages. We used conditional logistic regression models to estimate the association between qHPV vaccination and each pregnancy outcome across matched sets. qHPV vaccination status was included as the primary exposure. Multivariable models were additionally adjusted for county of residence, mothers' country of birth, highest educational level, annual household income level, smoking, body mass index, assisted reproduction, and maternal diagnoses.

We further assessed potential effect modification by age at qHPV vaccination (<17 v ≥ 17 years), using 17 years as the median age at first sexual intercourse among women in Sweden.³⁵ We modelled qHPV vaccination as a three category exposure: unvaccinated, vaccinated at <17 years of age, and vaccinated at ≥ 17 years of age. We used a Wald test to compare the adjusted log odds ratios for women vaccinated at ≥ 17 years of age versus <17 years of age. We further classified preterm birth into extremely preterm birth, very preterm birth, and moderate to late preterm birth on the basis of the WHO definition.³⁰ As an additional analysis to explore the potential pathway involving high grade cervical lesions and subsequent cervical treatment, we repeated the adjusted models with diagnosis of high grade cervical lesion included as an additional covariate, using it as a proxy for cervical treatment.

We handled missing data in covariates, including county of residence, maternal country of birth, highest educational level, annual household income level, smoking, and body mass index, by using multiple imputation by chained equations.³⁶ We generated 10 imputed datasets, did all analyses within each dataset, and combined them using Rubin's rules. Details of missing patterns, imputation models and diagnostics are provided in the supplementary materials.

As a sensitivity analysis, we assessed the associations between qHPV vaccination and pregnancy outcomes, as well as effect modification by age at human papillomavirus vaccination by using a population based cohort design to increase the statistical power marginally with the limitation of stronger residual confounding through conventional adjustment (supplementary materials). In the cohort analysis, we also estimated the number needed to treat by using model standardised predicted risks. We also did additional analyses in which each predefined maternal diagnosis was modelled separately as an individual binary variable rather than being combined into a single indicator. Finally, we did a sensitivity analysis in which stillbirths were retained in the definitions of other adverse pregnancy outcomes except neonatal mortality, to overcome uncertainty in the temporal ordering between fetal death and preterm labour and to assess the robustness of the main findings.

We report the odds ratios and adjusted odds ratios with 95% confidence intervals. We used SAS software version 9.4 for data management and Stata version 18.0 and R version 4.5.1 for statistical analyses. Statistical significance was set as $P < 0.05$.

Patient and public involvement

Patients and members of the public were not involved in the design, conduct, reporting, or dissemination plans of this research. No dedicated funding was available for patient and public involvement activities.

Results

Study population

Between 1 January 2006 and 31 December 2023, we identified 762 481 singleton births among nulliparous women aged 16-35 years in Sweden, of which 624 713 births met the inclusion criteria (fig 1). Among the eligible births, 92 620 (14.8%) women had received qHPV vaccination before pregnancy (table 1). Compared with unvaccinated women, vaccinated women were more likely to give birth in more recent calendar years, be younger at birth, and have a mother born in Sweden (table 1). In the study population, 0.4% were vaccinated with a high grade cervical lesion diagnosis before giving birth, compared with 3.1% unvaccinated with a previous high grade cervical lesion diagnosis (supplementary table S3). Across the matched case-control datasets (fig 1; supplementary table S4), each adverse pregnancy outcome was matched to approximately 10 controls per case, with the exceptions of PROM and SGA infant, for which the

Table 1 | Characteristics of primiparous women who had singleton birth, by human papillomavirus vaccination status before pregnancy. Values are numbers (percentages)

Characteristics	Vaccinated (n=92 620)	Unvaccinated (n=532 093)	Total (n=624 713)
Year of childbirth:			
2006-10	497 (0.5)	191 549 (36.0)	192 046 (30.7)
2011-15	8733 (9.4)	167 482 (31.5)	176 215 (28.2)
2016-19	30 233 (32.6)	103 977 (19.5)	134 210 (21.5)
2020-23	53 157 (57.4)	69 085 (13.0)	122 242 (19.6)
Maternal age at birth, years:			
16-19	3437 (3.7)	10 606 (2.0)	14 043 (2.2)
20-24	25 254 (27.3)	93 496 (17.6)	118 750 (19.0)
25-29	45 316 (48.9)	214 478 (40.3)	259 794 (41.6)
30-35	18 613 (20.1)	213 513 (40.1)	232 126 (37.2)
Mother's country of birth:			
Sweden	81 956 (88.5)	434 927 (81.7)	516 883 (82.7)
Others	10 143 (11.0)	80 098 (15.1)	90 241 (14.4)
Missing	521 (0.6)	17 068 (3.2)	17 589 (2.8)
Highest educational level*:			
Low	6964 (7.5)	42 257 (7.9)	49 221 (7.9)
Middle	35 338 (38.2)	203 520 (38.2)	238 858 (38.2)
High	50 160 (54.2)	285 337 (53.6)	335 497 (53.7)
Missing	158 (0.2)	979 (0.2)	1137 (0.2)
Highest household income level†:			
Low	55 101 (59.5)	318 687 (59.9)	373 788 (59.8)
Middle	24 021 (25.9)	135 478 (25.5)	159 499 (25.5)
High	13 481 (14.6)	77 482 (14.6)	90 963 (14.6)
Missing	17 (0.0)	446 (0.1)	463 (0.1)
Body mass index‡:			
Underweight, <18.5	2194 (2.4)	12 269 (2.3)	14 463 (2.3)
Normal, 18.5-24.9	51 656 (55.8)	306 608 (57.6)	358 264 (57.3)
Overweight, 25-29.9	22 652 (24.5)	118 730 (22.3)	141 382 (22.6)
Obese, ≥30	12 009 (13.0)	59 360 (11.2)	71 369 (11.4)
Missing	4109 (4.4)	35 126 (6.6)	39 235 (6.3)
Smoking§:			
Non-smoker	84 113 (90.8)	475 738 (89.4)	559 851 (89.6)
1-9 cigarettes/day	3147 (3.4)	24 675 (4.6)	27 822 (4.5)
≥10 cigarettes/day	418 (0.5)	4843 (0.9)	5261 (0.8)
Missing	4942 (5.3)	26 837 (5.0)	31 779 (5.1)
Assisted reproduction:			
No	88 191 (95.2)	498 060 (93.6)	586 251 (93.8)
Yes	4429 (4.8)	34 033 (6.4)	38 462 (6.2)
Maternal diagnoses¶:			
No	84 022 (90.7)	498 597 (93.7)	582 619 (93.3)
Yes	8598 (9.3)	33 496 (6.3)	42 094 (6.7)

*Educational level was assessed in year before childbirth and classified as "low" if individual had ≤9 years of primary education, "middle" if individual had 2-3 years of secondary schooling, and "high" if individual had post-secondary education and above.

†Household income level was assessed in year before childbirth and categorised as "low" if it was below 33rd centile, "middle" if it was from 33rd to 67th centile, and "high" if it was above 67th centile, determined on basis of three levels of annual household income derived from data for all Swedish people 20-65 years of age in year that income was assessed.

‡Body mass index was calculated from height and weight at first prenatal visit (usually at 8-12 weeks gestational age).

§Smoking was based on self-reported cigarette smoking at first prenatal visit (usually at 8-12 weeks gestational age).

¶Maternal diagnosis was considered to be any diagnoses of hypertension, diabetes, immunodeficiency and HIV infection, rheumatoid arthritis, inflammatory bowel diseases, cardiovascular diseases, systemic lupus erythematosus, or asthma noted by physician at time of discharge from hospital.

mean matching ratios were 7.87 and 7.19 controls per case, respectively.

Human papillomavirus vaccination and pregnancy outcomes

In the crude analyses (fig 2), qHPV vaccination was associated with lower odds of all included adverse pregnancy outcomes except PROM, compared with no vaccination. We observed statistically significant associations for the primary outcomes preterm birth (odds ratio 0.92, 95% confidence interval (CI) 0.89 to 0.96), extremely preterm birth (0.78, 0.66 to 0.92), very preterm birth (0.80, 0.71 to 0.91), moderate

to late preterm birth (0.95, 0.91 to 0.99), and sPTB (0.93, 0.89 to 0.97) and for the secondary outcomes SGA infant (0.92, 0.90 to 0.95), severe SGA infant (0.84, 0.80 to 0.89), and stillbirth (0.79, 0.66 to 0.93), compared with no vaccination.

After adjustment for all covariates (fig 2), qHPV vaccination was associated with lower odds of all included adverse pregnancy outcomes, compared with no vaccination. Statistically significant associations were observed for the primary outcomes preterm birth (adjusted odds ratio 0.95, 95% CI 0.91 to 0.99), very preterm birth (0.85, 0.75 to 0.97), and sPTB (0.95, 0.91 to 0.99), and for the secondary outcomes pPROM

Association between quadrivalent HPV vaccination and adverse pregnancy outcomes

Crude and adjusted odds ratios for adverse pregnancy outcomes associated with quadrivalent HPV vaccination before pregnancy



Crude odds ratios were based on cases and controls matched on maternal age at birth and calendar year of conception. Adjusted odds ratios were based on cases and controls matched on maternal age at birth and calendar year of conception, and additionally adjusted for county of residence, mother's country of birth for included women, highest educational level, highest annual household income level, smoking, body mass index, assisted reproduction and maternal diagnoses (any diagnoses of hypertension, diabetes, immunodeficiency and HIV infection, rheumatoid arthritis, inflammatory bowel diseases, cardiovascular diseases, systemic lupus erythematosus, or asthma)

■ Crude ■ Adjusted

Outcome	Cases	Controls	Cases (%) vaccinated	Controls (%) vaccinated		Odds ratio (95% CI)
Primary outcomes						
PTB	34 930	346 019	4914 (14.1)	50 845 (14.7)		0.92 (0.89 to 0.96)
						0.95 (0.91 to 0.99)
Extremely PTB	1784	17 662	252 (14.1)	2859 (16.2)		0.78 (0.66 to 0.92)
						0.88 (0.74 to 1.05)
Very PTB	3258	32 292	445 (13.7)	4996 (15.5)		0.80 (0.71 to 0.91)
						0.85 (0.75 to 0.97)
Moderate to late PTB	29 888	296 065	4217 (14.1)	42 990 (14.5)		0.95 (0.91 to 0.99)
						0.97 (0.93 to 1.01)
sPTB	25 966	259 260	3587 (13.8)	37 368 (14.4)		0.93 (0.89 to 0.97)
						0.95 (0.91 to 0.99)
Secondary outcomes						
pPROM	11 771	117 702	1719 (14.6)	17 602 (15.0)		0.96 (0.90 to 1.02)
						0.93 (0.87 to 1.00)
PROM	62 751	494 110	9680 (15.4)	74 651 (15.1)		1.04 (1.01 to 1.06)
						0.98 (0.95 to 1.01)
SGA (<10th centile)	73 139	526 049	10 111 (13.8)	78 171 (14.9)		0.92 (0.90 to 0.95)
						0.97 (0.95 to 1.00)
SGA (<3rd centile)	19 965	199 565	2622 (13.1)	28 948 (14.5)		0.84 (0.80 to 0.89)
						0.92 (0.87 to 0.97)
Stillbirth	1946	19 453	231 (11.9)	2658 (13.7)		0.79 (0.66 to 0.93)
						0.87 (0.73 to 1.04)
Neonatal mortality	802	8020	114 (14.2)	1228 (15.3)		0.88 (0.69 to 1.13)
						0.96 (0.74 to 1.24)

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CI=confidence interval; HPV=human papillomavirus; pPROM=preterm prelabour rupture of membranes; PROM=prelabour rupture of membranes at 37+ weeks; PTB=preterm birth; SGA=small for gestational age; sPTB=spontaneous preterm birth

Fig 2 | Association between quadrivalent human papillomavirus vaccination and adverse pregnancy outcomes. An interactive version of this graphic and downloadable data are available at <https://public.flourish.studio/visualisation/30147874/>

(0.93, 0.87 to 1.00) and severe SGA infant (0.92, 0.87 to 0.97).

After we included diagnosis of a high grade cervical lesion as an additional covariate, the estimates for preterm birth, sPTB, and pPROM were attenuated towards the null compared with the primary adjusted model, whereas estimates for other outcomes showed minimal change (supplementary figure S2).

Effect modification by age at human papillomavirus vaccination

Women vaccinated at <17 years of age had significantly lower odds of the primary outcomes, including preterm birth (adjusted odds ratio 0.90, 95% CI 0.85 to 0.95) and sPTB (0.89, 0.84 to 0.95), compared with unvaccinated women, after adjustment for all covariates (fig 3). For secondary outcomes, vaccination

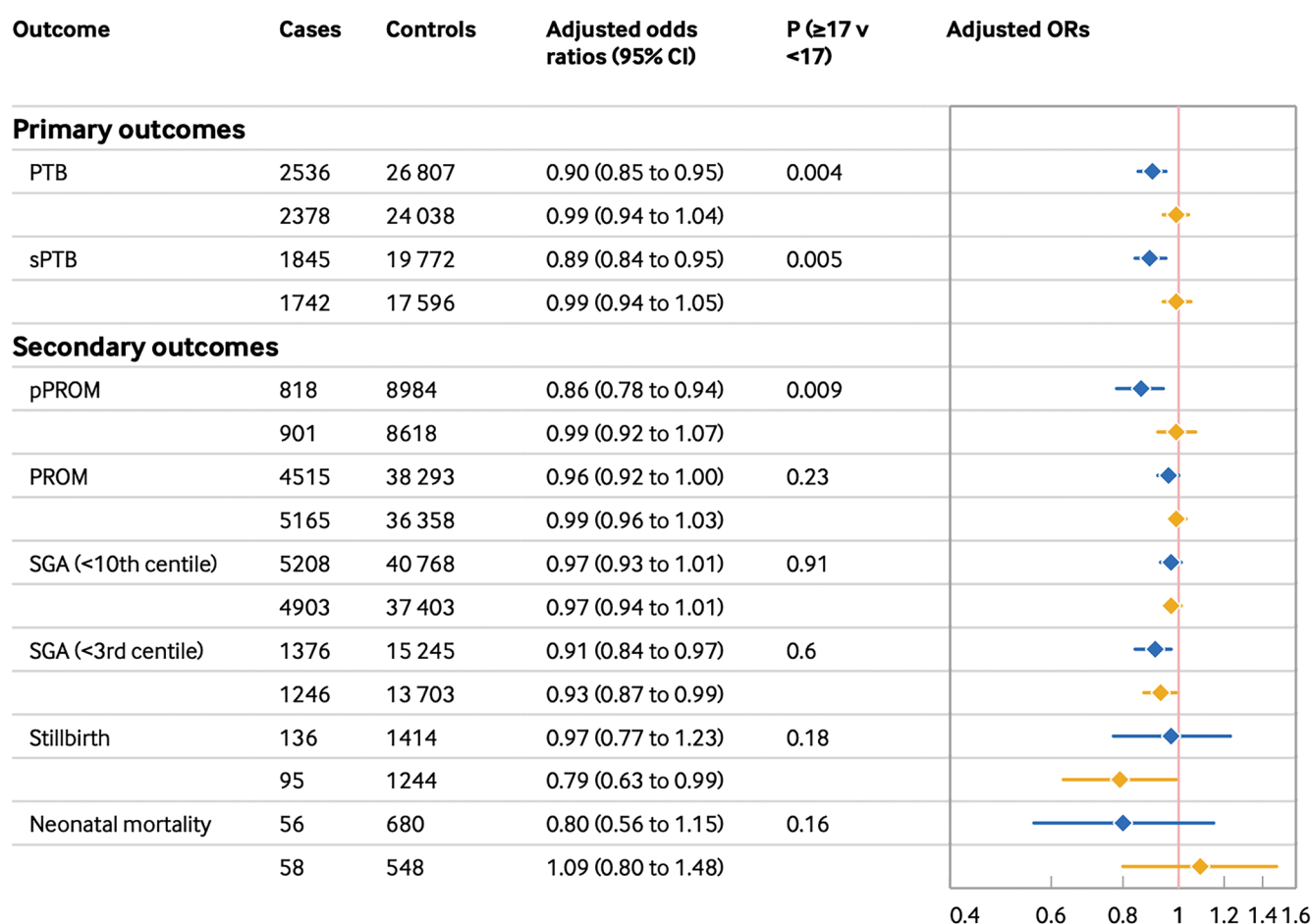
Quadrivalent HPV vaccination and pregnancy outcomes by vaccination age



Adjusted odds ratios for adverse pregnancy outcomes by age at quadrivalent HPV vaccination before pregnancy

Adjusted odds ratios were based on cases and controls matched on maternal age at birth and calendar year of conception, and additionally adjusted for county of residence, mother's country of birth for included women, highest educational level, highest annual household income level, smoking, body mass index, assisted reproduction and maternal diagnoses (any diagnoses of hypertension, diabetes, immunodeficiency and HIV infection, rheumatoid arthritis, inflammatory bowel diseases, cardiovascular diseases, systemic lupus erythematosus, or asthma). No HPV vaccination before pregnancy was treated as reference group. P value was derived from Wald test comparing adjusted log odds ratios for women vaccinated at ≥ 17 versus < 17 years of age

■ Vaccinated < 17 ■ Vaccinated ≥ 17



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CI=confidence interval; HPV=human papillomavirus; OR=odds ratio; pPROM=preterm prelabour rupture of membranes; PROM=prelabour rupture of membranes at 37+ weeks; PTB=preterm birth; SGA=small for gestational age; sPTB= spontaneous preterm birth

Fig 3 | Association between quadrivalent human papillomavirus vaccination and adverse pregnancy outcomes by age at vaccination. An interactive version of this graphic and downloadable data are available at <https://public.flourish.studio/visualisation/30176816/>

before age 17 was significantly associated with lower adjusted odds of pPROM (adjusted odds ratio 0.86, 0.78 to 0.94) and severe SGA infant (0.91, 0.84 to 0.97) (fig 3). By contrast, for women vaccinated at ≥ 17 years of age, we observed a significant association only with severe SGA infant (adjusted odds ratio 0.93, 0.87 to 0.99) and stillbirth (0.79, 0.63 to 0.99). Per outcome comparisons between women vaccinated at < 17 years and women vaccinated at ≥ 17 years of age show that, except for SGA infant and stillbirth, risk estimates were systematically lower for women vaccinated earlier; for outcomes including preterm birth ($P=0.004$), sPTB ($P=0.005$), and pPROM ($P=0.009$), these differences were statistically significant.

Sensitivity analyses

In analyses using a population based cohort design, results were largely consistent with the matched case-control analyses: adjusted odds ratios for all included adverse pregnancy outcomes were < 1 (supplementary table S5); women vaccinated at < 17 years of age had lower adjusted odds of preterm birth, sPTB, pPROM, PROM, and neonatal mortality than women vaccinated at ≥ 17 years of age (supplementary table S6). The estimated numbers needed to treat based on model standardised absolute risks ranged from 451 for severe SGA to 24 116 for neonatal mortality (supplementary table S7). The lowest numbers needed to treat were for severe SGA, preterm birth, PROM, sPTB, and SGA infant, corresponding to 451, 518, 538, 560, and 573 women, respectively. In addition, results were largely unchanged when each predefined maternal diagnosis was modelled separately as an individual binary variable (supplementary figures S3 and S4). Similarly, the sensitivity analysis retaining stillbirths in the definitions of other adverse pregnancy outcomes yielded results that were highly consistent with the primary analysis (supplementary figure S5).

Discussion

In this nationwide, population based study with individual level data linkage, we found that qHPV vaccination before pregnancy was associated with a reduced risk of adverse pregnancy outcomes after adjustment for a range of covariates, especially preterm related outcomes. The risk reduction was generally more pronounced among women vaccinated at earlier ages. By providing evidence for an association between human papillomavirus vaccination and reduced adverse pregnancy outcomes, we extend existing evidence and contribute to a more comprehensive understanding of the broader health implications of human papillomavirus vaccination. Together with previous research showing the safety of human papillomavirus vaccination during pregnancy,³⁷ our results suggest that human papillomavirus vaccination is not only safe with respect to pregnancy outcomes but may also confer additional benefits by reducing the risk of adverse events. Collectively, this evidence supports the global strategy for human papillomavirus

vaccination and its continued implementation in routine immunisation programmes.

Comparison with other studies

The observed risk reduction after human papillomavirus vaccination in our study is consistent with previous registry based and population level studies.^{19–22} Two Finnish studies based on a community randomised human papillomavirus vaccination trial with nationwide registry linkage reported lower rates of preterm birth among vaccinated women, particularly for early preterm birth.^{21 22} This evidence from a randomised setting suggests a potential protective effect of human papillomavirus vaccination on preterm birth; however, statistical power was limited by small numbers of pregnancies and follow-up restricted to early reproductive age. Additionally, a Danish study based on individual level linked national registries found that women vaccinated before age 17 years were at lower risk of sPTB than unvaccinated women, but those vaccinated after 17 years of age were not.¹⁹ A region based data linkage study conducted in Aberdeen, Scotland, ($n = 11\,174$) showed that human papillomavirus vaccination was not associated with preterm birth but was associated with lower risk of pPROM, PROM, pre-eclampsia, and antepartum haemorrhage, with substantial variations in effect size across outcomes.²³ Building on previous studies, our analysis additionally accounted for calendar year of conception through exact matching, which may capture temporal differences in availability and uptake of human papillomavirus vaccine, cervical screening practices, obstetric care, and pregnancy outcome ascertainment. At the population level, an ecological study from Australia reported that maternal cohorts with 60–80% human papillomavirus vaccination coverage experienced a 3.2% reduction in rates of preterm birth and a 9.8% reduction in births with SGA infants, estimates that are compatible with those observed in our study.²⁰

Possible underlying mechanisms

Two main pathways have been proposed to explain how human papillomavirus vaccination may reduce adverse pregnancy outcomes: a direct effect through prevention of human papillomavirus infection and an indirect effect through reduced need for cervical excisional treatment.^{18 19} Epidemiological evidence increasingly supports an association between maternal human papillomavirus infection and adverse pregnancy outcomes.^{5–9} A systematic review and meta-analysis reported a nearly twofold increased risk of preterm birth among women with genetically confirmed human papillomavirus infection during pregnancy⁶; other research also reported associations between exposure to human papillomavirus and intrauterine growth restriction and low birth weight.⁵ In addition, a population level study from Australia reported reductions in SGA infants in cohorts with higher human papillomavirus vaccination coverage, although residual confounding,

particularly by smoking, could not be excluded.²⁰ Experimental studies also suggest that exposure to human papillomavirus may impair early embryonic development and trophoblast function, indicating a potential role of human papillomavirus in abnormal placentation and preterm birth.^{38,39} Because placental derived fetal growth restriction is closely related to abnormal placentation and placental dysfunction, this pathway may also be relevant to fetal growth related outcomes such as SGA infants.⁴⁰

Regarding the indirect mechanism, population based studies consistently show that excisional treatment for high grade cervical lesions is associated with an approximately twofold risk of sPTB.^{11,41} A meta-analysis also showed significantly elevated risks of preterm birth, PROM, and low birth weight following cervical conisation.⁴² Together, these epidemiological, clinical, and experimental findings provide biologically plausible support for a protective role of human papillomavirus vaccination against adverse pregnancy outcomes. In our additional analysis using diagnosis of a high grade cervical lesion as an imperfect proxy for cervical treatment, adjustment for this variable attenuated the estimates for preterm birth, sPTB, and pPROM towards the null (supplementary figure S2). This pattern is consistent with the possibility that high grade cervical lesions and subsequent cervical treatment may contribute to the pathway linking human papillomavirus vaccination to preterm related outcomes. However, because diagnosis does not necessarily indicate that treatment occurred and does not capture treatment type or timing, this analysis should be interpreted as exploratory.

Although human papillomavirus vaccination was consistently associated with reduced risks of several adverse pregnancy outcomes in our study, the magnitude of risk reduction was modest. This may partly reflect that many post-vaccination births occurred among women vaccinated through opportunistic or catch-up programmes, some of whom may have already been exposed to human papillomavirus at the time of vaccination.⁴³ In addition, the low prevalence of high grade cervical lesions in our study population likely limited the potential impact of reduced cervical treatment on pregnancy outcomes, attenuating the observable effect size (supplementary table S3). Nevertheless, longer follow-up of vaccinated cohorts will include larger numbers of pregnancies and more complete observation of pregnancy outcomes across the reproductive life course, allowing future studies to better quantify these potential benefits.

Strengths and limitations of study

This population based study leveraged nationwide, high quality Swedish register data with long follow-up in a real world setting, minimising selection bias and misclassification and enabling assessment of both common and rare adverse pregnancy outcomes. Use of individual level data allowed adjustment for a broad range of measured confounders. In addition, the matched case-control design improved comparability

between vaccinated and unvaccinated women by matching on combinations of maternal age and calendar year, two key and correlated factors related to human papillomavirus vaccination uptake and pregnancy outcomes, while retaining statistical power through matching up to 10 controls per case. Sensitivity analyses based on the full cohort through adjustment for confounders yielded estimates comparable to those from the case-control analyses, supporting the robustness of the findings. Finally, assessment of effect modification by age at vaccination showed stronger associations among women vaccinated before 17 years of age, consistent with proposed mechanisms and suggesting additional benefits of timely, school based human papillomavirus vaccination for preventing adverse pregnancy outcomes.

We acknowledge several limitations. Firstly, although we adjusted for an extensive set of covariates, residual confounding cannot be entirely excluded owing to the observational nature of the study. In particular, modality and uptake of human papillomavirus vaccination could not be fully captured in the data, and residual confounding related to catch-up or opportunistic vaccination, previous human papillomavirus exposure, health seeking behaviour, and sexual or reproductive behaviour may remain, especially among women vaccinated at age 17 years or older. In addition, differences in use of interventions to prevent preterm birth, such as cervical cerclage, could not be fully assessed and may have contributed to residual confounding. Secondly, we were unable to assess spontaneous abortions before 22 gestational weeks, which represent a competing event for preterm birth and related outcomes, as such data are not available in the MBR. If late spontaneous abortions were more common among unvaccinated women, consistent with their higher observed risk of preterm birth, exclusion of these events may have attenuated the observed effect estimates. Thirdly, we excluded stillbirths from the analyses of other adverse pregnancy outcomes to avoid misclassifying births after fetal death as non-stillbirth adverse pregnancy outcomes, particularly for preterm related outcomes. However, we were unable to distinguish antepartum from intrapartum stillbirths or determine whether fetal death preceded or followed the onset of labour. Therefore, some overlap between intrapartum stillbirth and spontaneous preterm labour, particularly at very early gestational ages, cannot be excluded. Fourthly, lack of information on post-vaccination human papillomavirus infection and cervical treatment precluded investigation of underlying biological or clinical pathways. Although we used diagnosis of high grade cervical lesions as an imperfect proxy for cervical treatment in an additional analysis, this measure could not capture whether treatment occurred or treatment type. Therefore, this analysis was exploratory and could not establish the mechanism underlying the observed associations. Finally, despite the population based design and long follow-up, statistical power remained limited for certain rare outcomes, particularly stillbirth

and neonatal mortality. Regarding the generalisability of our findings, although the observed associations are supported by plausible biological pathways and existing epidemiological evidence, the generalisability of our findings may still be influenced by differences across settings in the prevalence of human papillomavirus infection and high grade cervical lesions, human papillomavirus vaccination coverage, and obstetric care, which may affect the contribution of the proposed pathways.

Policy implications

Beyond the established benefits of human papillomavirus vaccination in cancer prevention,¹⁶ the demonstrated reductions in adverse pregnancy outcomes associated with vaccination before conception may translate into substantial long term health and economic benefits. Individuals born preterm are known to have substantially higher healthcare use and costs across the life course,⁴⁴ suggesting that even modest reductions in preterm related outcomes could yield meaningful public health and healthcare system benefits. Consequently, given the introduction of gender neutral human papillomavirus vaccination,¹³ the observed population level reductions in human papillomavirus infection,⁴⁵ and the herd effect achieved through high vaccination coverage,⁴⁶ policy evaluations and cost effectiveness analyses should account not only for costs averted through cancer prevention but also for potential reductions in pregnancy related complications and their associated lifelong healthcare utilisation.

These potential additional benefits may be relevant not only for Sweden but also for other countries considering the introduction, expansion, or strengthening of human papillomavirus vaccination programmes. Including potential reproductive benefits in future policy evaluations may further shift the overall cost-benefit balance towards vaccination, including in settings where human papillomavirus vaccination has not yet been implemented. These findings may also inform future updates of national guidelines and broader global human papillomavirus vaccination strategies, in which reproductive outcomes could be considered as part of the wider public health value of human papillomavirus vaccination. Furthermore, by suggesting that human papillomavirus vaccination not only is safe with respect to adverse pregnancy outcomes but may also offer benefits beyond cancer prevention, these findings would help to strengthen public confidence in human papillomavirus vaccination. Looking ahead, continued long term follow-up of vaccinated populations, together with systematic monitoring of pregnancy and birth outcomes, will be important to further quantify these broader reproductive and societal impacts.

Conclusions

In this population based study, receiving qHPV vaccination before pregnancy was associated with lower risk of adverse pregnancy outcomes. Risk

reduction was generally greater among women vaccinated at earlier ages. These findings highlight the importance of timely immunisation through school based programmes and extend the benefits of human papillomavirus vaccination far beyond cancer prevention to the reduction of adverse pregnancy outcomes.

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Contributors: All authors contributed to the conceptualisation of the study. ZZ, AP, VS, NK, BJ, JD, CK, and JL contributed to the methodology. ZZ curated the data and did the formal analysis. ZZ and AP contributed to data visualisation. JL provided resources and led the investigation. AP, PS, CK, and JL supervised the study, and CK and JL were responsible for project administration. VS, PS, and JL acquired funding. ZZ wrote the original draft of the manuscript. All authors critically revised the manuscript, approved the final version for submission, and agree to be accountable for all aspects of the work. ChatGPT 5.2 (OpenAI) was used for language editing and code optimisation. JL is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Ethical approval: This study was approved by the Regional Ethical Review Board in Stockholm, Sweden (Dnr 02-556, 2011/921-32, and 2019-04397), which determined that informed consent by the study participants was not required.

Data sharing: The raw datasets are not publicly available owing to Swedish privacy laws and regulations. Access to individual level data from Swedish national registers is regulated by law and can be granted only following ethical review and approval by the relevant authorities in Sweden. More detailed information on the data can be requested from Swedish National Board of Health and Welfare (registerservice@socialstyrelsen.se) and Statistics Sweden (scb@scb.se). The analysis code for the manuscript is openly available at <https://doi.org/10.5281/zenodo.20794497>.

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

Dissemination to participants and related patient and public communities: Findings from this study will be shared with policy makers, professional organisations, and relevant patient and public

groups through several dissemination channels, including press communications, social media platforms, scientific conferences, and presentations at professional and stakeholder meetings, to support discussions on human papillomavirus vaccination policies and strategies to improve reproductive health.

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Web extra: Supplementary materials

Web extra: Statistical analysis plan