

A retrospective cohort study examining STI testing and perinatal records demonstrates reproductive health burden of chlamydia and gonorrhoea

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Summary: Reproductive health burden of STIs measured by pregnancy

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ABSTRACT

Adverse reproductive health outcomes, such as pelvic inflammatory disease, ectopic pregnancy, and tubal factor infertility, have been associated with *Chlamydia trachomatis* and *Neisseria gonorrhoea* infections. We propose that these reproductive health outcomes could be complemented by measuring subsequent pregnancies and assisted reproductive technologies to assess impact on fertility. The study design was a cohort study of women in Queensland (QLD), Australia, using data linkage methods to link chlamydia and/or gonorrhea testing records (including an unexposed group undergoing full blood count tests) (2000 and 2005) with the QLD Perinatal Registry (2000 to 2013). We used generalised additive modelling to determine the associations of chlamydia and/or gonorrhea testing history (and test results) with odds of subsequent pregnancy in comparison to the unexposed group. The cohort included 132 962 women, with 69 533 records of pregnancies. Women in the exposed group, with no prior pregnancy, had a reduced odds of a pregnancy than the unexposed group during the follow up of the study (20 year old (at 2005) aOR 0.91 95% CI 0.87-0.95, and 25 year old aOR 0.71 95% CI 0.68-0.75). Our data provides further evidence at a population level of the significant impact on reproductive outcomes associated with chlamydia and gonorrhea.

INTRODUCTION

Chlamydia trachomatis (chlamydia) and *Neisseria gonorrhoeae* (gonorrhea) are commonly diagnosed sexually transmitted infections (STI) that have been associated with serious reproductive health outcomes for women, and may cause obstetric or perinatal complications (Menon *et al.*, 2015, Lenz & Dillard, 2018). Obstetric or perinatal complications associated with STIs during pregnancy include preterm deliveries, preterm rupture of membranes, low birth weight, or still birth (Liu *et al.*, 2013, Heumann *et al.*, 2017, Reekie *et al.*, 2018). Tubal factor infertility and ectopic pregnancy have been associated with a history both STIs in numerous studies (Swasdio *et al.*, 1996, Hillis *et al.*, 1997, Barlow *et al.*, 2001, Bakken *et al.*, 2007, Goller *et al.*, 2018, Reekie *et al.*, 2019). Pelvic Inflammatory Disease (PID) has been strongly associated with both pathogens, and PID in turn increases the risk of ectopic pregnancy and tubal factor infertility (TFI) (Weström *et al.*, 1992, Hillis *et al.*, 1997, Low *et al.*, 2006, Simms *et al.*, 2006, Bakken & Ghaderi, 2009, Oakeshott *et al.*, 2010, Davies *et al.*, 2013, Davies *et al.*, 2014, Reekie *et al.*, 2014, Reekie *et al.*, 2018). Population level assessments, typically using data linkage approaches, have robustly established chlamydia and gonorrhea testing to be significant risk factor(s) for PID, even for some studies where test results have been negative (Davies *et al.*, 2013, Davies *et al.*, 2014, Reekie *et al.*, 2014, Davies *et al.*, 2018, Reekie *et al.*, 2018). However, PID is not a notifiable condition, diagnosis is subjective and may be inconsistent between different settings (Goller *et al.*, 2019).

In spite of the substantial proof for these reproductive health burdens, there is limited evidence evaluating subsequent pregnancy, which has been substantiated with a birth record, as an indicator of fertility after chlamydia or gonorrhea infections. We are aware of only one previous study that has evaluated pregnancy (as a measure of fertility), substantiated by a birth record, and associated with a history of chlamydia testing. This was a study of a Norwegian population

(n=20 762) that found no difference in odds of a pregnancy associated with chlamydial testing results (Bakken *et al.*, 2007). However, this study does not provide a comparison to an unexposed group who were not tested for chlamydia (Bakken *et al.*, 2007). Robust measure of pregnancy that has been substantiated by a birth record as an outcome measure would add to current understanding of the reproductive health burden from these STIs. We have used retrospective cohort study design to evaluate the association of pregnancy (via birth records) and perinatal outcomes (pre-term or low birth weight and still birth) with chlamydia and/or gonorrhea testing history and test results in women in the State of Queensland, Australia.

METHODS

Study design and data retrieval

We used a cohort study to investigate associations with chlamydia and gonorrhea testing history and pregnancy outcomes (using retrospective data linkage methodologies). The datasets used are based in the State of Queensland, Australia (~20% of Australian population). Our primary outcome was pregnancy defined as a record of birth in the Queensland Perinatal Registry. We used the birth record to define pregnancy because this provided a substantiated measure that a pregnancy had occurred. Secondary outcomes included perinatal outcomes of low birth weight (<2500g) and pre-term birth (before 37 weeks). Secondary outcomes were derived from the Queensland Perinatal Registry, and so analysis for these outcomes was restricted to women with a birth record (pregnancy).

We compiled the cohort by merging two datasets that we obtained from AUSLAB, the Queensland Health Clinical and Scientific Information System. Our cohort included two

groups of women: 1) an exposed group that comprised women who had had a chlamydia or gonorrhoea test between 2000 and 2005; and 2) an unexposed group that comprised women who had a full blood count laboratory investigation but no chlamydia and/or gonorrhoea test between 2000 and 2005. Records of tests for chlamydia and/or gonorrhoea, conducted in all public pathology laboratories in QLD between January 1st, 2000 and December 31st 2005 for women aged between 15 and 31 were collated (Median age 24; IQR 21 – 26, at Dec 31st 2005). The unexposed group comprised women aged 15-31 years old (Median age 24; IQR 21 – 27, at Dec 31st 2005) who underwent a full blood count test (independent of indications for the test) in the same five year period and with no record of testing for chlamydia and/or gonorrhoea during the study period (Figure 1). Entry into the exposed group was defined as having any testing history to chlamydia and/or gonorrhoea, as women who access testing services have characteristics that are more likely to result in a positive diagnosis. Previous studies using PID as an outcome measure have also found that women with a testing history, but no positive diagnosis experience increased risk of PID (Reekie *et al.*, 2018). Further analysis also was used to compare women in the exposed group by their diagnosis results, by classification into distinct groups based on testing status (negative or positive) and number of tests. Full blood count was selected as our unexposed because these were women who were also in contact with primary care and also did not have a test record in our data for chlamydia and/or gonorrhoea. The FBC has a range of indications, but both FBC and STI screening can be used during antenatal or preparation for pregnancy investigations, therefore, analysis also included pregnancy during the testing window (Troussard *et al.*, 2014). Deterministic methods were used to remove any women from the full blood count group that also appeared in the chlamydia and/or gonorrhoea testing dataset.

We linked the testing dataset with the Perinatal Data Collection (Queensland Health Statistics Unit) that records all births in Queensland. The perinatal dataset included all birth entries from 01/01/2000 until 30/06/2013. The perinatal data included the mother's date of birth, the baby's date of birth, birth weight, gestational weeks of the pregnancy, and stillbirth.

< Figure 1 goes here >

Linkage methodologies

First name, middle name (if available), surname, sex, and date of birth were used for linking the AUSLAB datasets with the Queensland Perinatal Registry. Linkage was deterministic in the case when information matched exactly, and probabilistic methods were used in the remaining cases. The linkage framework does not have a published error rate, but has a similar design to the Western Australia and New South Wales systems which have reported error rates of 0.11% and 0.3% respectively (New South Wales Government, 2012, Queensland Government, 2017). Women whose data were unable to be linked with the Queensland Perinatal Registry were assumed to have no births during the study time frame. Multiple linkages (n=2702) were randomly assigned a single linkage in the dataset (Supplemental Data S1 and Supplementary Figure S1). Women with missing postcode information (n=19764), or a postcode from outside of Queensland were removed (n=4525). Thirty women without a date of birth were excluded. All women with a recorded birth that occurred before the test record during the 2000-2005 test were excluded. All person-records were assigned a de-identified code and the data were provided to the study investigators after linkage and de-identification.

Statistical Methods

We used generalised additive modelling to determine the association between chlamydia and/or gonorrhoea testing history (and test results) and each outcome. Information about the testing dates for women in the unexposed group, and women with only a negative test result was not available, which restricted any valid time-to-event analysis. Analysis assessed the odds of pregnancy in a discrete outcome period. Age was modelled with a restricted cubic spline with three knots and interacted with pregnancy in the testing period and exposure status, in order to evaluate the impact of association as a function of follow-up time relative to age. Models were adjusted for age, pregnancy in the testing period, socioeconomic status, and location (a measure of access to health services (Welfare, 2019)). Entry into the cohort was based on testing records in AUSLAB (either chlamydia and/or gonorrhoea test [exposed] or blood test [unexposed]) in 2000 to 2005. The cohort was followed up to assess for birth and secondary outcomes (birth weeks, birth weight) until 30/06/2013. The study analysed only the first recorded birth for each woman. We converted birthweight ($\pm 2500\text{g}$) and birth weeks (± 37 weeks) to binary outcomes for the purposes of this study, using values from World Health Organisation standards [10]. Postcodes were used to classify the socio-economic area of the women, defined as low, middle or high using the ABS Index of Relative Socio-economic Disadvantage, and to classify regionality as living in a major city, regional or remote geographical area (Statistics, 2005). If a woman had multiple testing events the first postcode recorded was used. Location was then defined as the combination of socioeconomic status and regionality, to account for the interaction effect between an area's socioeconomic status and overall access to health services.

Data preparation and analysis was completed using the **R** software version 3.6.3. The code used for this analysis can be found at github.com/torricallan/QLDPregnancyStudy.

Ethical approval

This study was reviewed and approved by the Metro North Hospital and Health Service Human Research Ethics Committee (approval number HREC/14/QPCH/85).

RESULTS

The cohort comprised 132 962 women after linkage, refinement, and exclusions (Figure 1, Supplementary Table S1). The women in the cohort were aged between 22 and 39 years at the study completion, June 30th 2013, (Median 31; IQR 28-34). Overall, 24 702 (18.6%) women were tested for chlamydia and/or gonorrhoea (exposed), including, 20 871 (15.7%) women who had only negative tests(s), 3 237 (2.4%) who had a single positive test recorded, and 594 (0.4%) who had multiple positive tests recorded. The unexposed group included 108 260 women. A total of 69 533 (52.3%) women in the cohort had a pregnancy during the study time frame (Figure 1). A total of 37 495 (28.1%) women in the cohort had a pregnancy during the testing window (2000-2005), and 43 325 (32.5%) had a pregnancy during the outcome period (2006-2013).

<Figure 2 goes here>

Women in the exposed group with no prior pregnancy in the testing period (2000-2005) had varying odds of having a pregnancy depending on their age at the end of the outcome period (Figure 2). Younger women (aged 20 in 2005, no pregnancy during testing window) had slightly reduced odds of pregnancy in the outcome window compared to same women in the unexposed group (aOR 0.91; 95% CI 0.87 – 0.95), whereas the reduction in the chances of

having a pregnancy for women aged 25 in 2005 was larger (aOR 0.71; 95% CI 0.68 – 0.75) (Table 1).

<Table 1 goes here>

When investigating the association between the classification of tests within the exposure group and pregnancy, we found that women with all negative tests had reduced odds of pregnancy compared to women with a single positive test when they were aged 20 in 2005 and had no pregnancy in the testing period. However, for women that were older at the end of the testing period, there was no discernible distinction to be made between women with a single positive test and women with all negative tests. Women with multiple positive tests had chances of pregnancy in the outcome window that were comparable with women in the unexposed group. The association between the type of the infection for women with a positive test (chlamydia only, gonorrhoea only, chlamydia and gonorrhoea) showed that women aged 25 with no pregnancy in the testing period, had reduced odds of pregnancy in the outcome window if they tested positive for chlamydia (aOR 0.70; 95% CI 0.62 – 0.79). The odds ratio for women testing positive for gonorrhoea in this group was higher and the confidence interval was wide (aOR 0.78; 95% CI 0.50 – 1.21). Women with positive results for both pathogens were comparable to all women in the exposed group, and the odds of pregnancy was influenced by age (Figure 3, Table 2).

<Figure 3 goes here>

Amongst women with a pregnancy in the testing period, women in the exposed group had increased odds of having a pregnancy in the outcome window. This difference was most

pronounced for younger women. Women with a pregnancy in the testing period also had increased chances of a pregnancy in the outcome window if they had a single positive test compared to all negative tests (Figure 2), and greater chances again if they had multiple positive tests. Women with a pregnancy during the testing window that had a gonococcal infection had increased chances of pregnancy in the outcome window compared to women with a chlamydial infection.

<Table 2 goes here>

The women who had a history of chlamydia and /or gonorrhoea testing were more likely to have adverse perinatal outcomes such as low birth weight and pre-term birth (Table 2). Women with multiple positive tests had significantly higher odds of the low birth weight outcome compared to women with single positive tests and all negative tests. The odds of pre-term birth were comparable between all testing groups.

DISCUSSION

In a study of 132 962 women in Queensland, Australia, we have measured the reproductive outcomes for women with a history of testing for chlamydia and gonorrhoea. We have investigated how future pregnancies depend on the presence or absence of a testing history, the number of tests, the diagnosis of these tests, and the infection. We have also shown that the association between testing history and odds of future pregnancy is dependent on the age at which women are exposed to a test, and if they had any pregnancy during the same time frame as their testing history. This is the first large study using data-linkage to test an association of any recorded subsequent pregnancy with a history of testing for these two STIs.

A strength of our study is the large sample size, an order of magnitude larger than the only other study to look at subsequent pregnancy as an outcome measure (Bakken *et al.*, 2007), and is a similar order of magnitude to studies that have established the association of chlamydial testing history with PID (Low *et al.*, 2006, Bakken & Ghaderi, 2009, Davies *et al.*, 2016, Reekie *et al.*, 2018) and tubal factor infertility (Reekie *et al.*, 2019). A further strength of our study is the inclusion of both chlamydia and gonorrhoea, and an unexposed group, unlike the only prior study to test for the association with infertility by measuring subsequent pregnancies. Women in the exposed group had reduced odds of pregnancy compared to the unexposed group, when they had no prior pregnancy in the testing period, and they were aged within the middle of the distribution of ages at the end of the testing period.

There are limitations of our study that should be considered. The timeframe of the cohort did not cover full reproductive years for the women, although it did extend beyond the median age of first birth in QLD in 2013 (28.5; (Statistics, 2013)) as the cohort median of age 31 (IQR 28-34) at study completion. There were 50 185 notifications of chlamydial and gonococcal infections in Queensland from 2000-2005 (including all ages and genders) (Health, 2019), so our data represents ~12% of all infections in this time period for this state. We were unable to account for people who had moved out of the study area prior to pregnancies although 2005 census data reported limited migration out of the state so we expect this to have only a small impact (Statistics, 2005). We have adjusted for location and socioeconomic status, however, these factors still may be over-represented in the exposed (tested) group relative to the unexposed group. Relying solely on pathology data and the few associated demographic details means we have no information regarding behavioral and lifestyle predictors of those undergoing STI testing, which risks further confounding of results and difficult interpretation. Further, we were unable to assess the physicians' decision-making process when identifying

women for testing, and therefore not able to account for the significance of provider-initiated testing as opposed to patient-initiated testing. It is also possible that women recorded in the perinatal database (which covers both public and private hospitals) may have had chlamydia and gonorrhea tests not recorded in the AUSLAB dataset (government funded testing only). The unexposed group selection was for women who had full blood count test done but no chlamydia and gonorrhea test recorded in AUSLAB. Without knowledge as to why these women were tested, this raises the possibility of further selection bias. The study data did not include dates of tests, or all incidences of negative tests, preventing a temporal analysis that may have provided a richer understanding of the findings.

A previous analysis of population characteristics has established that women who access testing services for chlamydia have lower condom usage and higher numbers of sexual partners, and that these characteristics were more likely to result in chlamydia positivity for women with a testing history compared to a general population (Riha J, 2011). Our findings suggest that STI testing may be indicative of risk behaviors that may predispose individuals to infection and consequently greater adverse outcomes. Care must be taken in interpreting our results to determine the exact reproductive burden of these two STIs, as our definition of exposure implies that women in the exposed group are more sexually active and potentially more likely to have a pregnancy than women in the unexposed group. The youngest women in our data had comparable odds of pregnancy between exposed and unexposed groups, however older women in the exposed group had reduced odds. Similarly, younger women with a single positive test had higher chances of pregnancy compared to women with all negative tests. However, there was no distinction between the two for older women. Women with multiple positive tests, women with both chlamydia and gonorrhea infections, and women with a testing history that had a pregnancy in the testing window were more likely to have a pregnancy in the

outcome window. However, it is important to consider these results in the light of the known differences in health outcomes and STI incidences for Indigenous Australians. The data on Indigenous identity was not available for the unexposed group and is likely to be a confounding factor that has particularly contributed to the increased odds of pregnancy results for multiple infections, especially as indigenous women are more likely to test positive to chlamydia and gonorrhoea, and more likely to have younger pregnancies (Graham *et al.*, 2012, Utz, 2014).

Women in the exposed group had increased odds of pre-term births and low birth-weight outcomes. Further, women with a single positive test had odds ratio of both outcomes that were greater than the comparable estimates for women with all negative tests. Although the 95% Confidence Intervals do overlap, this supports the increased reproductive burden of a positive test diagnosis, in comparison to only negative tests, as it agrees with previous findings using outcomes of PID and tubal factor infertility (Davies *et al.*, 2013, Davies *et al.*, 2014, Reekie *et al.*, 2014, Davies *et al.*, 2018, Reekie *et al.*, 2018).

CONCLUSION

We report a relationship between a history of chlamydia or gonorrhoea testing history in women with reduced odds of having a subsequent pregnancy indicating that these two infections continue to represent a reproductive health burden.

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Figure legends

Figure 1. Summary of cohort. The cohort was formed using data linkage methodologies between a testing dataset and perinatal dataset as outlined in the figure.

Figure 2. Cohort Summary. (A) The distribution of ages grouped by exposure group (B-D) Comparison of the 1st percentile, median and 9th percentile values for the age distribution for exposure groups (E) Proportion of the cohort in each location and SES category by exposure (F) Proportion of the cohort with a pregnancy in the testing period by exposure.

Figure 3: Association of chlamydia and gonorrhoea testing and pregnancy. (A) Compares exposed and unexposed group (B) Compares single positive test, all negative tests and unexposed group (C) Compares Chlamydia positive, Gonorrhoea positive and unexposed group. All lines represent the predicted probability of having a pregnancy in the outcome period, and the shaded area represents the (endpoint transformed) 95% confidence interval.

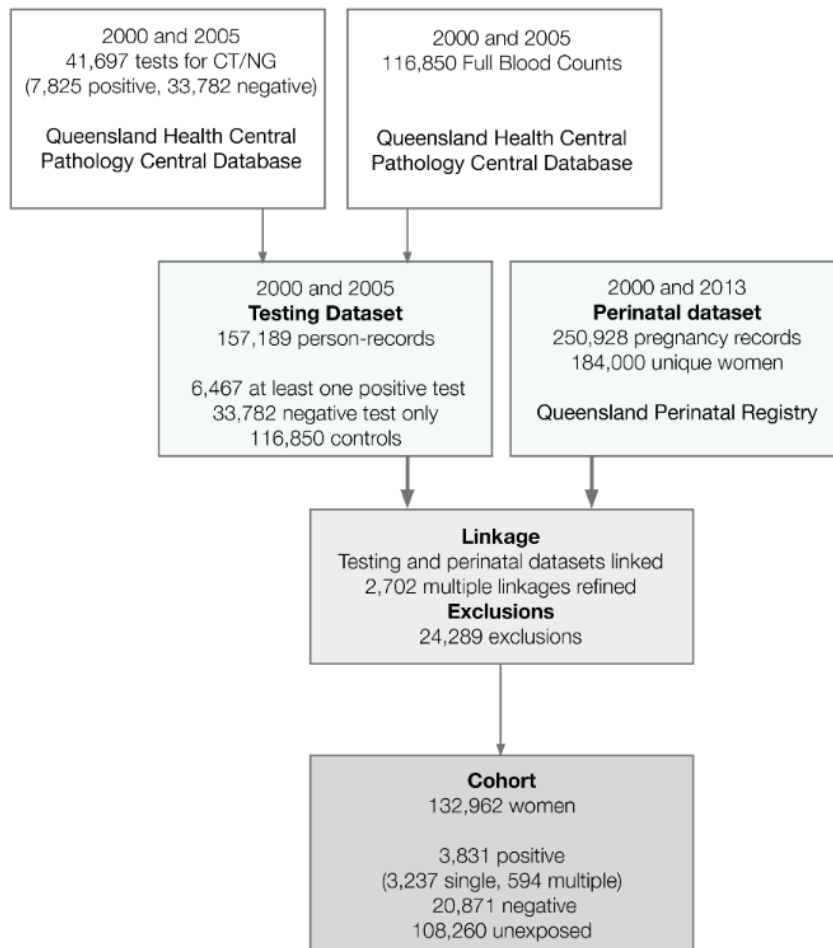


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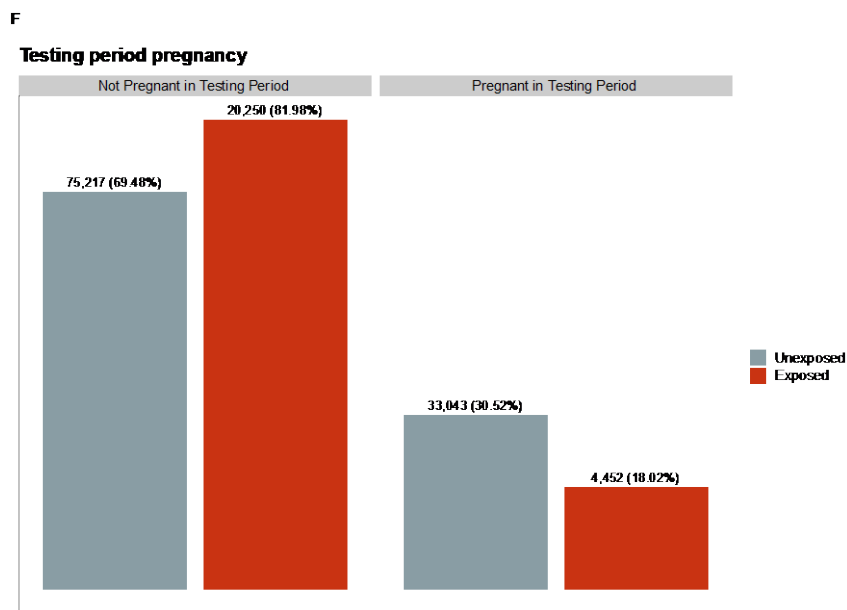
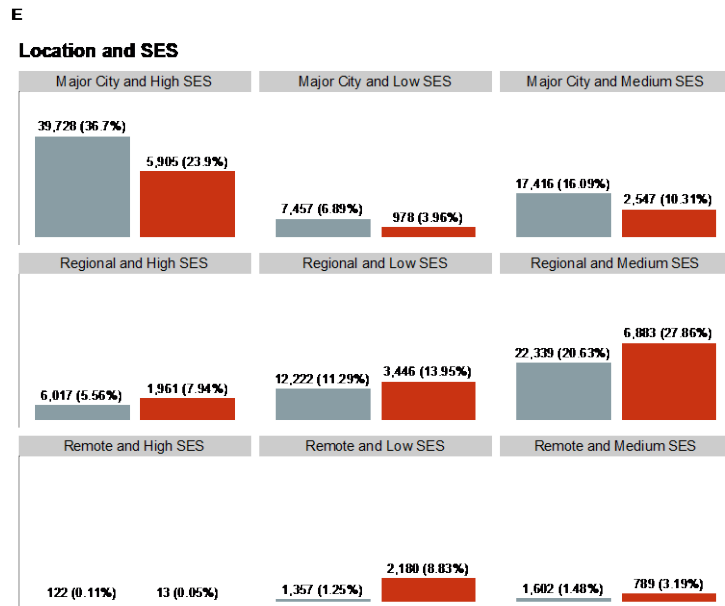
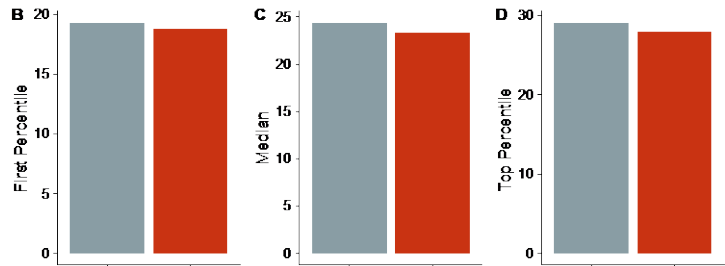
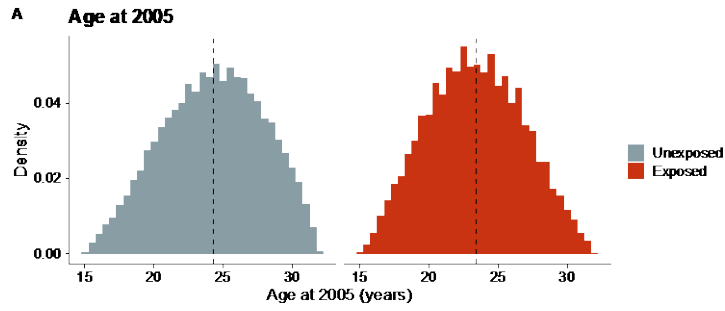


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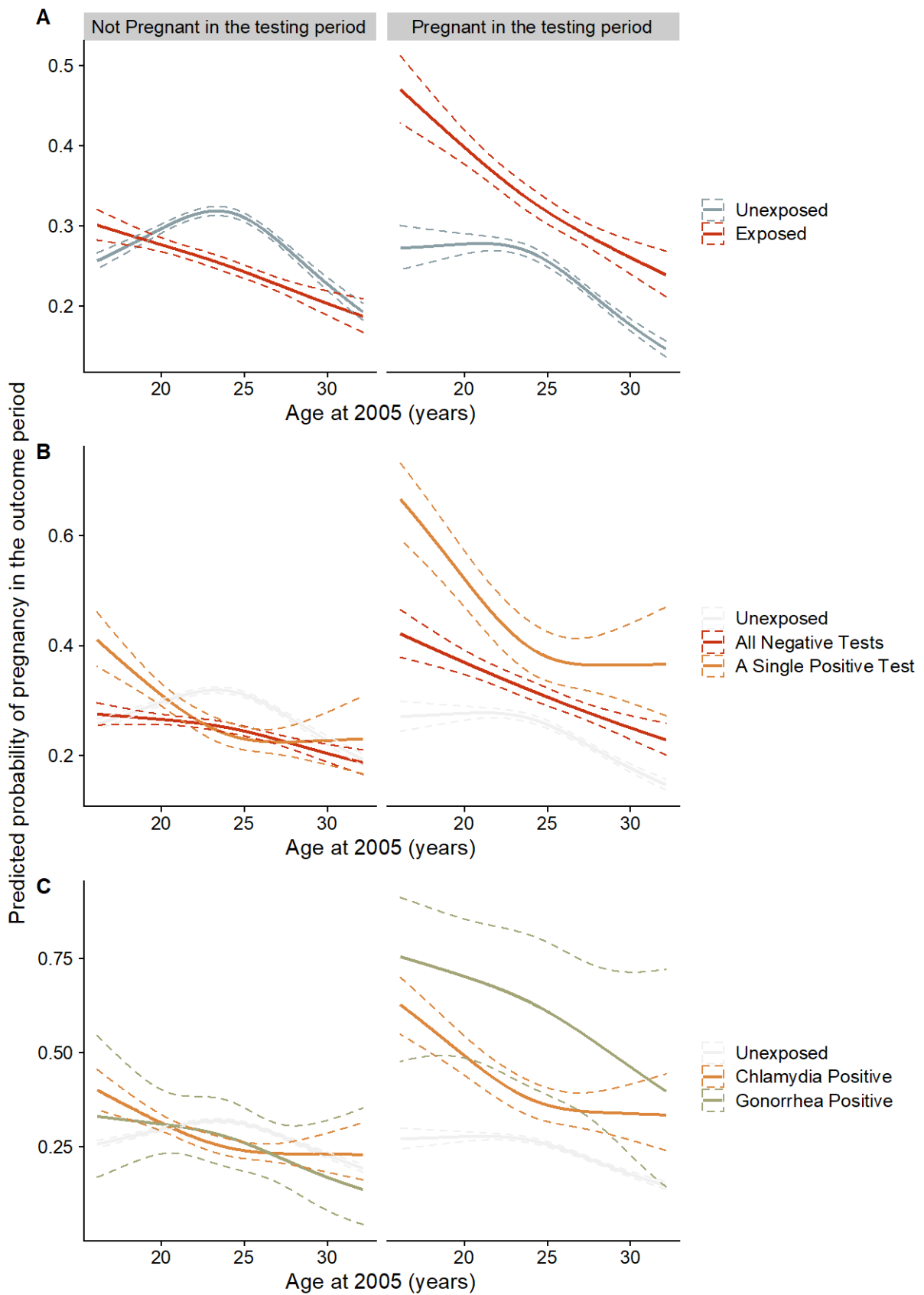


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the shaded area represents the (endpoint transformed) 95% confidence interval.

Table 1: Odds ratios of pregnancy in the outcome period.

		aOR ^a (95% CI)		aOR (95% CI)		aOR (95% CI)
Not Pregnant in the testing period						
Aged 20 at end of testing period	Exposed^b (n = 20, 250)	0.91 (0.87, 0.95)	Multiple Positive Tests (n = 468)	1.51 (1.20, 1.90)	CT (n = 2,500)	1.08 (0.98, 1.20)
			Single Positive Test (n = 2,756)	1.07 (0.97, 1.17)	NG (n = 171)	1.06 (0.71, 1.59)
Aged 25		0.71 (0.68, 0.75)	All Negative Tests (n = 17,026)	0.86 (0.82, 0.90)	CT/NG (n = 553)	1.35 (1.11, 1.65)
			Multiple Positive Tests	1.04 (0.81, 1.35)	CT	0.70 (0.62, 0.79)
			Single Positive Test	0.66 (0.59, 0.75)	NG	0.78 (0.50, 1.21)
Aged 30		0.87 (0.79, 0.95)	All Negative Tests	0.72 (0.68, 0.75)	CT/NG	0.81 (0.63, 1.04)
			Multiple Positive Tests	0.90 (0.40, 2.03)	CT	1.01 (0.76, 1.36)
			Single Positive Test	1.00 (0.76, 1.31)	NG	0.69 (0.30, 1.60)
			All Negative Tests	0.87 (0.78, 0.96)	CT/NG	0.91 (0.43, 1.93)
	Unexposed (n = 75, 217)	1 (ref)	Unexposed	1 (ref)	Unexposed	1 (ref)
Pregnant in the testing period						
Aged 20 at end of testing period	Exposed (n = 4,452)	1.72 (1.59, 1.86)	Multiple Positive Tests (n = 126)	4.17 (2.72, 6.40)	CT (n = 463)	2.53 (2.06, 3.11)
			Single Positive Test (n = 481)	2.85 (2.33, 3.40)	NG (n = 27)	6.17 (2.47, 15.40)
			All Negative Tests (n = 3,845)	1.53 (1.40, 1.67)	CT/NG (n = 117)	6.13 (3.92, 9.59)
Aged 25		1.35 (1.26, 1.45)	Multiple Positive Tests	2.89 (1.97, 4.24)	CT	1.64 (1.35, 1.99)

		Single Positive Test	1.77 (1.47, 2.15)	NG	4.53 (1.84, 11.14)
Aged 30	1.64 (1.48, 1.83)	All Negative Tests	1.28 (1.19, 1.38)	CT/NG	3.66 (2.43, 5.51)
		Multiple Positive Tests	2.50 (1.07, 5.83)	CT	2.37 (1.70, 3.31)
		Single Positive Test	2.67 (1.95, 3.65)	NG	3.99 (1.38, 11.60)
		All Negative Tests	1.55 (1.39, 1.74)	CT/NG	4.14 (1.88, 9.13)
	Unexposed	Unexposed	1 (ref)	Unexposed	1 (ref)
	(n = 33,043)				

^a All models are adjusted for location and pregnancy in the testing period interacted with a cubic spline of age evaluated at 20, 25, and 30 (as at 2005)

^b Any history of testing for chlamydia/gonorrhea

Table 2: Perinatal Outcomes associated with a history of STI testing and test results

	aOR ^a (95% CI)		aOR (95% CI)
Pre-Term Birth			
Exposed^b (n = 8,144)	1.28 (1.18, 1.39)	Multiple Positive Tests (n = 290)	1.21 (0.81, 1.81)
		Single Positive Test (n = 1,202)	1.37 (1.14, 1.66)
		All Negative Tests (n = 6,652)	1.27 (1.16, 1.39)
Low Birth Weight			
Exposed	1.35 (1.23, 1.48)	Multiple Positive Tests	2.61 (1.85, 3.69)
		Single Positive Test	1.50 (1.23, 1.84)
		All Negative Tests	1.29 (1.17, 1.43)

^a Models adjusted for presence of the outcome (pre-term birth or low birth weight) in the testing period, a cubic spline of age (at 2005) with 3 knots, mother's age at birth and location

^b Any history of testing for chlamydia/gonorrhea