Risk of reproductive complications following chlamydia testing: a population-based retrospective cohort study in Denmark

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Summary

Background Uncertainty in the risk of reproductive complications (pelvic inflammatory disease, ectopic pregnancy, and tubal factor infertility) following chlamydia infection and repeat infection hampers the design of evidence-based chlamydia control programmes. We estimate the association between diagnosed chlamydia and episodes of hospital health care (inpatient, outpatient, and emergency department) for a reproductive complication.

Methods We constructed and analysed a retrospective population-based cohort of women aged 15–44 years from administrative records in Denmark (1995–2012). We used a subset of the national Danish Chlamydia Study. The master dataset contains all residents of Denmark (including Greenland) who had a positive chlamydia test recorded by a public health microbiology laboratory from Jan 1, 1992, to Nov 2, 2011. Individuals were randomly matched (by age and sex) to four individuals drawn from the population register (Danish Civil Registration System) who did not have a positive chlamydia test during this interval. The outcomes in the study were hospital episodes of health-care (inpatient, outpatient, and emergency department) with a diagnosis of pelvic inflammatory disease, ectopic pregnancy, or tubal factor infertility.

Findings The 516 720 women (103 344 positive, 182 879 negative, 230 497 never-tested) had a mean follow-up of 7·96 years. Compared with women with only negative tests, the risk of each complication was 30% higher in women with one or more positive tests (pelvic inflammatory disease, adjusted hazard ratio [AHR] 1·50 [95% CI 1·43–1·57]; ectopic pregnancy, AHR 1·31 [1·25–1·38]; tubal factor infertility, AHR 1·37 [1·24–1·52]) and 60% lower in women who were never-tested (pelvic inflammatory disease, AHR 0·33 [0·31–0·35]; ectopic pregnancy, AHR 0·42 [0·39–0·44]; tubal factor infertility AHR 0·29 [0·25–0·33]). A positive test had a minor absolute impact on health as the difference in the lifetime incidence of complications was small between women who tested positive and those who tested negative (pelvic inflammatory disease, 0·6%; ectopic pregnancy, 0·2%; tubal factor infertility, 0·1%). Repeat infections increased the risk of pelvic inflammatory disease by a further 20% (AHR 1·20, 95% CI 1·11–1·31).

Interpretation A single diagnosed chlamydia infection increased the risk of all complications and a repeat diagnosed infection further increased the risk of pelvic inflammatory disease. Therefore, control programmes must prevent first and repeat infections to improve women's reproductive health.

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Introduction

Chlamydia trachomatis is the most common bacterial sexually transmitted infection in Europe.[1] Many settings have introduced widespread chlamydia testing, which aims to reduce the incidence and prevalence of infection and the occurrence of reproductive complications (pelvic inflammatory disease, ectopic pregnancy, and tubal factor infertility). However, there is uncertainty about the risk of complications following the predominantly asymptomatic infections that are identified by this approach.[2–4]

This uncertainty poses a challenge for health-care workers providing prognostic information to those offered testing.[5] It might compromise resource allocation decisions informed by estimates of the clinical and cost-effectiveness of chlamydia control strategies from mathematical models that include estimates of this risk. Mathematical models commonly assume that 22% of women with an untreated chlamydia infection will progress to pelvic inflammatory disease[6] (assumed to be within 1 year) and of these, 8% will have an ectopic pregnancy, and 11% will develop infertility (not specifically tubal factor infertility).[7–12] These estimates are based largely on historical clinical studies. Population-based studies in settings with widespread chlamydia control suggest that the lifetime risk of pelvic

Research in context

Evidence before this study

We searched PubMed from Jan 1, 2008, to April 1, 2016, for studies that report the prospective risk of reproductive complications in low-risk women following chlamydia infection compared with a chlamydia-negative control group. We used the search term "*Chlamydia trachomatis*" combined with "pelvic inflammatory disease", "salpingitis", "endometritis", "infertility", or "ectopic pregnancy" and identified relevant studies restricted to the English language. We added these results to relevant studies identified by a 2010 systematic review and a study from the reference list of an included publication. The prospective risk of pelvic inflammatory disease following untreated genital chlamydia infection, treated infection, and a negative chlamydia test is presented in a single randomised controlled trial of 2529 women at low risk (9·5%, 1·6%, and 1·3%, respectively). However, the sample size is too small to detect a difference between groups in this secondary analysis. No prospective studies of the risk of ectopic pregnancy or infertility following untreated chlamydia infection were identified. Five retrospective cohort studies compare the lifetime risk of reproductive complications by chlamydia exposure in the general population. These studies show a 30–70% increased risk of pelvic inflammatory disease in women who test positive for chlamydia compared with women who test negative. The three studies of ectopic pregnancy have not reached consensus and the single study of infertility uses data from before the widespread introduction of highly sensitive diagnostic tests. There is limited information on the role of repeat infection in reproductive complications.

Added value of this study

This cohort is considerably larger than the examples in the published literature and it is representative of the population of a country. It uses contemporary chlamydia test methods and the never-tested cohort has a straightforward definition: women who do not have a chlamydia test during the cohort period. The size of the cohort has allowed us to report the contribution of a repeat diagnosed chlamydia infection to all three reproductive complications (pelvic inflammatory disease, ectopic pregnancy, and tubal factor infertility) for the first time in a single population.

Implications of all available evidence

Women with at least one diagnosed chlamydia infection have a 30% increased risk of pelvic inflammatory disease, ectopic pregnancy, and tubal factor infertility throughout their reproductive lifetime. The duration of the elevated risk of pelvic inflammatory disease is longer than the estimated 1 year duration of untreated chlamydia infection. Therefore, in the case of pelvic inflammatory disease, chlamydia is likely to act as a proxy for other risk factors of adverse reproductive health (eg, sexual behaviour, repeat chlamydia infection) or a diagnostic bias. The absolute impact of diagnosed chlamydia infections on reproductive complications might be small. We observed a small difference in the lifetime cumulative incidence of pelvic inflammatory disease, ectopic pregnancy, and tubal factor infertility between women who tested positive compared with women who tested negative. Women tested for chlamydia, who are negative, have an increased risk of complications compared with women who are never-tested. This finding might indicate that widespread testing in Denmark is targeting the at-risk population. The risk of pelvic inflammatory disease following chlamydia infection is increased by a further 20% following a repeat diagnosed infection but we found no evidence that repeat infections further increase the risk of ectopic pregnancy or tubal factor infertility. Control interventions need to prevent first infections to reduce the lifetime risk of pelvic inflammatory disease, ectopic pregnancy, and tubal factor infertility, and repeat infections to further reduce the risk of pelvic inflammatory disease.

inflammatory disease in women with diagnosed (and presumably treated) chlamydia is less than 15% (Uppsala, Sweden: 5·6% [95% CI 4·7–6·7];[5] Sør-Trøndelag, Norway: 1·1% [0·8–1·4];[13] Manitoba, Canada: 14·8%[14]). The lifetime risks of ectopic pregnancy and tubal factor infertility following pelvic inflammatory disease have not been reported using this study design, but the risks following chlamydia infection are low (ectopic pregnancy: Uppsala, 2·7% [95% CI 2·1–3·5];[5] Sør-Trøndelag, 0·8% [0·5–1·1];[15] and infertility: Uppsala, 6·7% [5·7–7·9][5]).

There is a consistent 30–70% increased risk of pelvic inflammatory disease in women who test positive for chlamydia compared with women who test negative,[5,13,14] but there is no consensus on the equivalent risk of ectopic pregnancy (Uppsala, adjusted hazard ratio [AHR] 1·3 [95% CI 0·9–1·7];[5] Sør-Trøndelag, AHR 1·1 [1·0–1·1];[15] Northern Jutland, Denmark, AHR 0·6 [0·3–0·9][16]), one estimate of the risk of infertility (Uppsala, AHR 1·31 [1·09–1·57][5]), and no estimates of the risk of tubal factor infertility. Additionally, there is limited information on the risk of complications after repeat infection.

Consensus estimates of the risk of complications following chlamydia are necessary for clinical consultations and chlamydia control policy decisions. Since the 1970s, Denmark has had a comprehensive electronic population register that can be linked to electronic health-care records and a well established chlamydia control programme with voluntary reporting of cases since 1984. We used a national cohort to improve estimates of the contemporary association between diagnosed chlamydia and pelvic inflammatory disease, ectopic pregnancy, and tubal factor infertility in women in Denmark, including never-tested women and after repeat diagnosed infections.

Methods

Dataset and data selection

We used a subset of the national Danish Chlamydia Study (appendix). The master dataset contains all residents of Denmark (including Greenland) who had a positive chlamydia test recorded by a public health microbiology laboratory from Jan 1, 1992, to Nov 2, 2011. Individuals were randomly matched (by age and sex) to four individuals drawn from the population register (Danish Civil Registration System [CRS register]) who did not have a positive chlamydia test during this interval. Controls could have had negative chlamydia tests. The unique ten-digit identification number for each individual in the cohort was used to extract demographic information (age, sex, postcode) from the CRS register; time interval of residence in Denmark from the CRS register; complete chlamydia test history from the public health microbiology laboratory data; and records of hospital health care (inpatient, outpatient, emergency department) from the Danish National Patient Registry (DNPR).

For this analysis, the master dataset was limited to women resident in Denmark (excluding Greenland) who entered the dataset after Jan 1, 1995, when aged 15–44 years, and who were in a five-person set (one chlamydia-positive and four chlamydia-negative or never tested) who met the study chlamydia exposure definitions. This start date was chosen because chlamydia notification became compulsory in Denmark in 1994 and in 1994–95 the DNPR changed from International Classification of Disease (ICD)-9 to ICD-10 coding and added outpatient and emergency department presentations. Individuals with a positive chlamydia test entered the cohort on the date of their first positive test during the study period. Their four matched individuals were assigned the same entry date.

During the study period, chlamydia diagnostic methods varied between laboratories and the change from non-nucleic acid methods to nucleic acid amplification tests (NAATs) occurred predominantly in 1999–2000. Records with an invalid or missing date, site, or result were removed along with tests not done on genital, rectal, or urinary samples. Where multiple eligible tests were recorded on the same date, positive results were retained in preference to negative results. Chlamydia tests were then restricted to one per 30-day period. The exposure in this study is chlamydia status and women were defined as chlamydia-positive if their first test in the study cohort was positive, negative if they had at least one negative test, and no positive tests during the follow-up period or never-tested if they did not have a recorded test during follow-up.

Outcomes

The outcomes in this study were hospital episodes of health-care (inpatient, outpatient, and emergency department) with a diagnosis of pelvic inflammatory disease (ICD-10 A18·1; A51·4; A52·7; A54·2; A56·1; N70-74·8), ectopic pregnancy (O00·00-00·9), or tubal factor infertility (N97·1). These data were added to the dataset. Follow-up continued until Oct 31, 2012. Women were censored on the first of the following events: emigration, death, 45th birthday, or their first hospital presentation with the relevant complication of interest.

See Online for appendix

Statistical analysis

We calculated the crude cumulative incidence of each complication by the end of follow-up (defined as the number of women diagnosed with the complication by the end of follow-up divided by the number of women at baseline). We constructed Kaplan-Meier survival plots of time to each complication by chlamydia exposure status and used Cox proportional-hazards regression to explore the association between chlamydia exposure status and each complication separately, adjusted for age at cohort entry, and year of entry. Negative women formed the baseline group and time since entry was the time axis.

We then divided the follow-up period of positive women into the interval following their first positive test and the interval following their second positive test and estimated the association between this repeat diagnosed

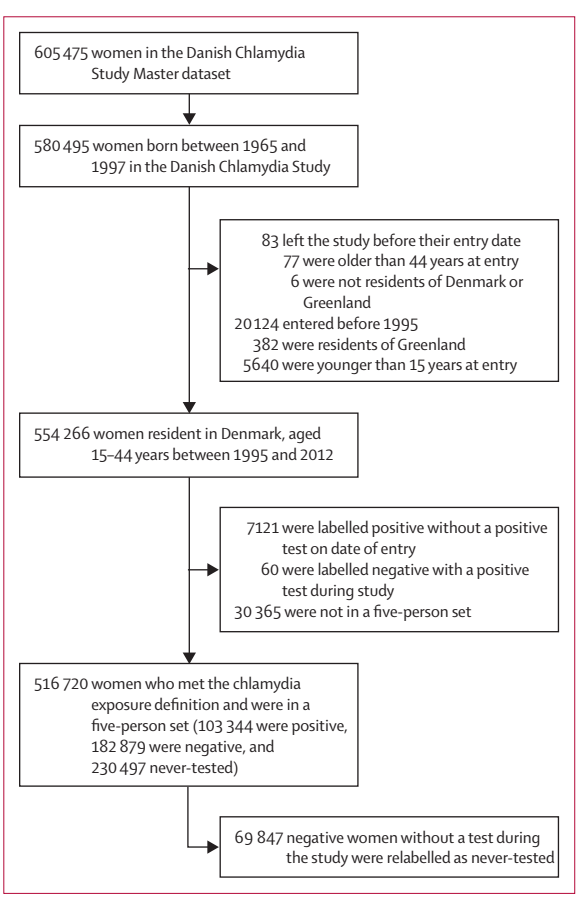


Figure 1: **Formation of the study cohort from the Danish Chlamydia Study master dataset**

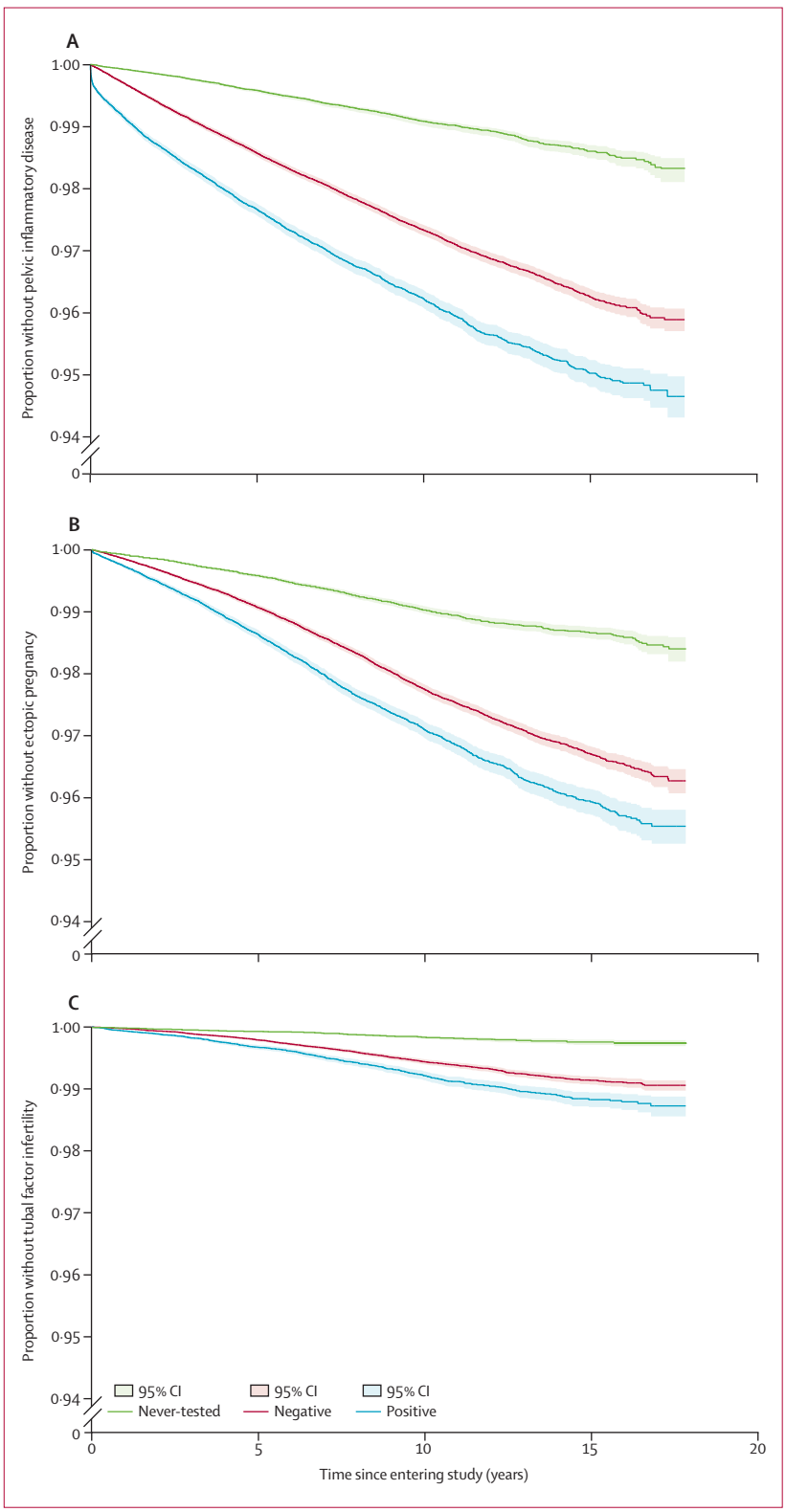


Figure 2: **Kaplan-Meier plots of time (years) to outcome by chlamydia exposure status**
Pelvic inflammatory disease (A), ectopic pregnancy (B), and tubal factor infertility (C).

chlamydia infection and each complication separately. Statistical analysis was done using STATA SE 11.2 (StataCorp LP, College Station, TX, USA).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

There were 516 720 women (103 344 [20%] positive, 182 879 [35%] negative, and 230 497 [45%] never-tested) in the study cohort (figure 1). The mean age at cohort entry was 22·4 years (SD 5·0; range 15·0–45·0), mean duration of follow-up was 8·0 years (median 7·2 years, range 1 day to 17·8 years, IQR 4·5–11·0), and total duration of follow-up was 4 114 502 person-years.

The crude cumulative incidence of pelvic inflammatory disease in the study was 3·1% (95% CI 3·02–3·23; 3214 of 103 344) in positive women, 2·5% (2·41–2·55; 4538 of 182 879) in negative women, and 0·6% (0·57–0·63; 1380 of 230 497) in never-tested women. The cumulative incidence of ectopic pregnancy was 2·2% (95% CI 2·14–2·33; 2307 of 103 344) positive, 2·0% (1·97–2·10; 3722 of 182 879) negative, and 0·6% (0·58–0·64; 1399 of 230 497) never-tested. The cumulative incidence of tubal factor infertility was 0·6% (95% CI 0·54–0·63; 605 of 103 344) positive, 0·5% (0·48–0·54; 930 of 182 879) negative, and 0·1% (0·09–0·12; 242 of 230 497) never-tested.

Women with an outcome on the date they entered the cohort were then excluded from the relevant analyses (pelvic inflammatory disease, n=459; ectopic pregnancy, n=52; tubal factor infertility, n=7). The rate of pelvic inflammatory disease was 403 per 100 000 person-years (95% CI 389–417) in positive women, 266 per 100 000 person-years (258–274) in negative women, and 89 (84–94) per 100 000 person-years in never-tested women. The rate of ectopic pregnancy was 284 per 100 000 person years (95% CI 273–296) in positive women, 217 per 100 000 person-years (210–224) in negative women, and 90 per 100 000 person-years (86–95) in those never-tested. The rate of tubal factor infertility was 74 per 100 000 person-years (95% CI 68–80) in positive women, 54 per 100 000 person-years (50–57) in negative women, and 16 per 100 000 person-years (14–18) in never-tested women.

Kaplan-Meier survival curves are presented in figure 2. The adjusted hazard of each outcome was 31–50% higher in women who tested positive compared with women who tested negative (pelvic inflammatory disease, AHR 1·50 [95% CI 1·43–1·57]; ectopic pregnancy, AHR 1·31 [1·25–1·38]; and tubal factor infertility, AHR 1·37 [1·24–1·52]), and 58–71% lower in women who were never-tested compared with women who tested negative

	Pelvic inflammatory disease			Ectopic pregnancy			Tubal factor infertility		
	Crude HR (95% CI)	Adjusted* HR (95% CI)	p value	Crude HR (95% CI)	Adjusted* HR (95% CI)	p value	Crude HR (95% CI)	Adjusted* HR (95% CI)	p value
Chlamydia									
Never	0·32 (0·30–0·34)	0·33 (0·31–0·35)	<0·0001	0·43 (0·40–0·45)	0·42 (0·39–0·44)	<0·0001	0·30 (0·26–0·35)	0·29 (0·25–0·33)	<0·0001
Negative	1	1		1	1		1	1	
Positive	1·48 (1·42–1·55)	1·50 (1·43–1·57)	<0·0001	1·33 (1·26–1·40)	1·31 (1·25–1·38)	<0·0001	1·41 (1·27–1·56)	1·37 (1·24–1·52)	<0·0001
Age (years)									
15–19	1	1		1	1		1	1	
20–24	1·13 (1·07–1·18)	1·06 (1·01–1·12)	0·0132	1·37 (1·30–1·45)	1·36 (1·29–1·44)	<0·0001	2·56 (2·21–2·97)	2·39 (2·07–2·77)	<0·0001
25–29	1·18 (1·11–1·25)	1·17 (1·10–1·24)	<0·0001	1·52 (1·42–1·62)	1·58 (1·48–1·69)	<0·0001	4·69 (4·03–5·47)	4·65 (3·99–5·42)	<0·0001
30–44	1·09 (1·00–1·18)	1·25 (1·15–1·35)	<0·0001	1·06 (0·96–1·17)	1·19 (1·08–1·32)	0·0007	4·85 (4·05–5·80)	5·69 (4·76–6·81)	<0·0001
Year									
1995–2000	1	1		1	1		1	1	
2001–07	0·79 (0·75–0·83)	0·83 (0·79–0·88)	<0·0001	1·00 (0·95–1·06)	1·08 (1·02–1·14)	0·0071	0·68 (0·61–0·75)	0·74 (0·66–0·82)	<0·0001
2008–12	0·62 (0·58–0·66)	0·79 (0·74–0·84)	<0·0001	0·97 (0·90–1·05)	1·26 (1·16–1·36)	<0·0001	0·43 (0·36–0·52)	0·62 (0·52–0·75)	<0·0001

*Adjusted for chlamydia exposure, age at entry to cohort, and year of entry to cohort.

Table 1: **Crude and adjusted hazard ratios (HRs) of pelvic inflammatory disease, ectopic pregnancy, and tubal factor infertility by chlamydia exposure status**

(pelvic inflammatory disease, AHR 0·33 [0·31–0·35]; ectopic pregnancy, AHR 0·42 [0·39–0·44]; and tubal factor infertility, AHR 0·29 [0·25–0·33]; table 1).

In the positive group, 23 011 (22·3%) women had one or more further positive chlamydia tests during follow-up. The risk of pelvic inflammatory disease was 20% higher following a second diagnosed infection compared with a first diagnosed infection (AHR 1·20, 95% CI 1·11–1·31) but the risk was unchanged for ectopic pregnancy (AHR 1·09, 0·99–1·20) and tubal factor infertility (AHR 1·06, 0·85–1·31; table 2).

	Pelvic inflammatory disease		Ectopic pregnancy		Tubal factor infertility	
	Adjusted* HR (95% CI)	p value	Adjusted* HR (95% CI)	p value	Adjusted* HR (95% CI)	p value
Diagnosed infections						
1	1		1		1	
≥2	1·20 (1·11–1·31)	<0·0001	1·09 (0·99–1·20)	0·0918	1·06 (0·85–1·31)	0·6115
Age (years)						
15–19	1		1		1	
20–24	0·81 (0·74–0·87)	<0·0001	1·07 (0·97–1·18)	0·1725	2·24 (1·75–2·88)	<0·0001
25–29	0·78 (0·70–0·87)	<0·0001	1·18 (1·05–1·33)	0·0064	3·97 (3·05–5·17)	<0·0001
30–44	0·99 (0·86–1·13)	0·8699	0·98 (0·83–1·17)	0·8315	5·82 (4·34–7·80)	<0·0001
Year						
1995–2000	1		1		1	
2001–07	0·75 (0·69–0·81)	<0·0001	1·05 (0·95–1·16)	0·3096	0·67 (0·56–0·81)	<0·0001
2008–12	0·59 (0·53–0·66)	<0·0001	1·06 (0·92–1·21)	0·4171	0·54 (0·40–0·73)	<0·0001

*Adjusted for chlamydia exposure, age at entry to cohort, and year of entry to cohort.

Table 2: **Adjusted hazard ratios (HRs) of pelvic inflammatory disease, ectopic pregnancy, and tubal factor infertility following a repeat chlamydia diagnosis**

Discussion

In this cohort of women from a contemporary setting with widespread chlamydia control who were tested for chlamydia, a positive chlamydia test increased the risk of pelvic inflammatory disease, ectopic pregnancy, and tubal factor infertility by at least 30%. This risk remained throughout 17 years of follow-up, which is considerably longer than the estimated 1 year duration of chlamydia infection.[17] Therefore, the (treated) index infection might, in part, be a marker for other risk factors for pelvic inflammatory disease. The impact of the index positive chlamydia test on reproductive health was small in absolute terms because the difference between the lifetime risks (cumulative incidence) of each outcome between women who tested positive and negative were small (0·1–0·6%). Finally, repeat diagnoses were a risk factor for pelvic inflammatory disease but not ectopic pregnancy or tubal factor infertility. These findings suggest that the optimal strategy for improving women's long-term reproductive health is to provide interventions that prevent both first and repeat infections.

This nationally representative cohort of over 500 000 women is an order of magnitude larger than previously published cohorts (Uppsala, 43 715;[5] Sør-Trøndelag, 24 947;[13] North Jutland, 13 693;[16] Manitoba, 72 883[14]). The size of the cohort together with the high volume of repeat testing allowed us to explore the risk of complications in never-tested women and following repeat diagnosed infections. There was complete ascertainment of chlamydia tests and hospital presentations for pelvic inflammatory disease, ectopic pregnancy, and tubal factor infertility in Denmark throughout the study.

In common with similar studies, there is an unquantifiable misclassification bias in chlamydia and outcome status.[5,13–15] We used chlamydia test records to assign lifetime chlamydia status but undiagnosed infections are likely to have occurred.[5] Misclassification of outcome status is likely to be most marked for pelvic inflammatory disease in which the diagnostic criteria

are non-specific, there is no gold-standard non-invasive diagnostic test,[18] and a diagnostic bias towards pelvic inflammatory disease in women with a past history of chlamydia.[2] This proposed diagnostic bias would increase the association between chlamydia and pelvic inflammatory disease if it affected hospital episodes of health care and could contribute to the observed increased risk of pelvic inflammatory disease after a repeat diagnosed infection.

Primary care data were not available in this study. This incomplete ascertainment of complications is likely to have had the greatest impact on the analysis of pelvic inflammatory disease where there has been a steady increase in management in the outpatient or community setting.[19,20] If there is no association between the cause of pelvic inflammatory disease and clinical presentation then the absence of cases managed solely in primary care will reduce the cumulative incidence but not change the relative risk across exposure groups. However, pelvic inflammatory disease due to chlamydia might have a milder clinical presentation than other causes.[21] If pelvic inflammatory disease in chlamydia-negative women is more likely to be recorded in the DNPR this would underestimate the association between chlamydia and pelvic inflammatory disease. This is unlikely to be relevant in this study because *Neisseria gonorrhoea*, a major cause of severe pelvic inflammatory disease, is rare in Denmark (80% of the 490 patients with gonorrhoea in Denmark in 2011 were men).[22]

There is uncertainty in the validity of our ICD definitions to accurately represent a relevant diagnosis in the clinical record. This uncertainty has been well documented for pelvic inflammatory disease[23–25] but might be less pronounced for ectopic pregnancy and tubal factor infertility because they have more specific diagnostic criteria. To improve validity, we restricted the cohort to women who entered after 1995 when ICD-10 coding was introduced, and emergency department and outpatient data were added to the DNPR. This period also coincided with the shift from voluntary to compulsory notification of chlamydia in 1994.

The structure of the study cohort was a trade-off between the completeness of exposure and outcome measures and the duration of follow-up. By starting on Jan 1, 1995, it was possible for the youngest women (at study entry) to reach the mean age of first childbirth in Denmark by the end of follow-up, although they did not reach the end of their reproductive lifetime. Exposure and outcome ascertainment was also comprehensive. The validity of a chlamydia test result will have changed following the introduction of NAATs in 1999–2000. NAATs have a high sensitivity compared with enzyme immunoassays and direct immunofluorescence tests. However, the pathogenicity of detected infections might vary with test type and be lowest for NAATs. In support of this, infection resolution rates have been shown to be higher in people diagnosed by the use of NAATs compared with enzyme immunoassay or culture.[26] Therefore, the association between diagnosed infections and reproductive complications might alter over time as the predominant diagnostic test changes.

To control for this, we adjusted the analysis for year of entry to the cohort. We were unable to control for many potential confounders, including sexual behaviour, reproductive intent, and sexual network, due to the absence of suitable data. We chose to include all women in our analysis of ectopic pregnancy rather than restricting the cohort to women who had a recorded pregnancy. This might explain the lower AHR of ectopic pregnancy following diagnosed chlamydia observed in women aged 30–44 years at cohort entry compared with women aged 25–29 years. Specifically, the rate of conception is likely to be lower in the older age group, and therefore if the true risk of ectopic pregnancy as the outcome of pregnancy is the same across age groups, the AHR would be lower in older women if the incidence of pregnancy was lower.

We used the Cox proportional hazards model in this study. This standard non-parametric method for modelling time-to-event data was used in the five comparator cohort studies.[5,13–16] The assumption of proportional hazards was violated in our analysis but this was not unexpected given the structure of our dataset: events at baseline are likely to become poorer predictors of events that occur after increasing time intervals. We explored several alternative methods for analysing the data;[27] however, we felt it was appropriate to report the findings of this Cox regression to enable direct comparison of the risk of complications in Denmark to other settings.

Our findings of an increased risk of pelvic inflammatory disease in chlamydia-positive women compared with chlamydia-negative women (AHR 1·50, 95% CI 1·43–1·57) is consistent with AHR estimates from comparable population-based cohorts (Uppsala, 1·27 [1·04–1·55];[5] Sør-Trøndelag, 1·69 [1·21–2·37];[13] and Manitoba, 1·55 [1·43–1·70])[14] despite differences in cohort structure, definition of chlamydia exposure, and pelvic inflammatory disease ascertainment. This increased risk is present throughout the reproductive lifetime and therefore the index chlamydia test is likely, at least in part, to be a surrogate for other risk factors for pelvic inflammatory disease, most likely undiagnosed sexually transmitted infections, including repeat chlamydia infections, which might be mediated through sexual or health-care seeking behaviour.

There is conflicting evidence in the literature about the relation between a chlamydia diagnosis and ectopic pregnancy. We found that a positive test increased the risk of ectopic pregnancy (as the outcome of any pregnancy) by 31% (AHR 1·31, 95% CI 1·25–1·38) compared with women with a negative test. This finding is consistent with the other study that included all women (Uppsala, AHR 1·26, 0·94–1·67).[5] Two further

studies limited their analysis to the first pregnancy in women with a pregnancy during follow-up and found a 45% decreased risk (Northern Jutland, AHR 0·55, 95% CI 0·31–3·59)[16] and 7% increased risk (Sør-Trøndelag, 1·07, 1·01–1·12).[15]

Chlamydia is thought to be a risk factor for tubal factor infertility rather than infertility more widely, and this is the only retrospective cohort study that has restricted the definition of infertility to tubal factor infertility. As tubal factor infertility is a subset of the overall infertility diagnoses it is expected that the cumulative incidence of tubal factor infertility would be lower than the cumulative incidence of infertility and we report a ten times lower cumulative incidence of tubal factor infertility compared with that of infertility in Uppsala. It is difficult to explain the similar increased HR for tubal factor infertility and infertility in chlamydia-positive compared with chlamydia-negative women in the two cohorts (Denmark, AHR 1·37 [95% CI 1·24–1·52]; Uppsala, 1·31 [1·09–1·57]).[5]

In this cohort, women with a diagnosed (and presumably treated) chlamydia infection had a low absolute risk of complications (cumulative incidence in positive women: pelvic inflammatory disease, 3·1%; ectopic pregnancy, 2·2%; tubal factor infertility, 0·6%) that was only slightly higher than that observed in women with a negative test (0·1–0·6% higher in positive than negative women). This information might provide reassurance to women who have a chlamydia test. However, this difference in risk is equivalent to 9·1–19·3% of the recorded complications in positive women. Therefore, chlamydia control interventions that prevent first infections and retain women in the lifetime-negative cohort could have an important effect on reproductive health.

In Denmark, widespread chlamydia testing appears to have been effectively targeted to women at risk of reproductive complications because the observed risks in never-tested women were extremely low. Nonetheless, some never-tested women did experience complications and might have missed out on appropriate health care. We observed a much lower risk of all complications in this group (compared with negative women) than the Uppsala study (eg, pelvic inflammatory disease: AHR 0·32 [95% CI 0·30–0·34] in Denmark and 0·72 [0·63–0·82] in Uppsala.)[5] This finding might reflect differences in the definition of the never-tested cohorts (lifetime never-tested in Demark compared with the interval before the first test in Uppsala) or an increased uptake of testing in Denmark due to the more recent time period.

This study adds substantially to the evidence that a repeat diagnosis of chlamydia further increases the risk of pelvic inflammatory disease[14,28] and we observed a very similar increased risk following a second diagnosed infection (11–31%) to the cohort in Manitoba (13–23%).[14] Unlike in Sør-Trøndelag we did not find that a repeat diagnosed infection was a risk factor for ectopic pregnancy but this could reflect differences in study definitions (including cohort and ectopic pregnancy) rather than biological differences.[15] Our observation that a repeat diagnosed infection was only a risk factor for pelvic inflammatory disease could be because each episode of chlamydia carries a discrete risk of pelvic inflammatory disease, whereas damage to the oviducts, sufficient to cause ectopic pregnancy and tubal factor infertility, might occur before the median duration of a first infection.

A single diagnosed chlamydia infection increases the risk of all reproductive complications in women and a repeat diagnosis further increases the risk of pelvic inflammatory disease. To improve women's long-term reproductive health and wellbeing, chlamydia control programmes must be designed to prevent both first and repeat infections. To inform the design of widespread chlamydia control interventions, more information is required on the relative contribution of chlamydia control activity (ie, interventions that reduce the incidence of untreated infections), change in the incidence of gonorrhoea, and change in the pathogenicity of diagnosed chlamydia infections after the introduction of NAATs[29] on the risk of reproductive complications.

Contributors

BD, KMET, MF, HWa, TB, and HWe contributed to study design, data interpretation, and writing. BD and KMET did the data analysis. MF, TB, HWe, SR, and the Danish Chlamydia Study Group designed the Danish Chlamydia Study and collected the dataset. MF cleaned the Danish Chlamydia Study dataset. MTM provided statistical advice and contributed to data interpretation and writing. Members of the Danish Chlamydia Study Group additionally contributed to writing.

Declaration of interests

BD and HWa declare personal fees from the European Centre for Disease Prevention and Control (ECDC). KMET declares personal fees from Aquarius Population Health. MF, SR, and MTM declare no competing interests. TB declares personal fees from GlaxoSmithKline, Bristol Myers Squibb, Gilead, Symphogen, and Abbvie, and grants from Pfizer. HWe declares grants from Roche Molecular, grants and personal fees from Hologic, and personal fees from Novo Nordic.

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