

Population excess fraction of ectopic pregnancy due to *Chlamydia trachomatis* infection in Finland

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1 Population excess fraction of Ectopic Pregnancy due to *Chlamydia trachomatis* in Finland

2 Rantsi *et al*¹ present results from a large high quality prospective population based case control
3 study nested within the Finnish maternity cohort. In the largest ever study of its kind they examine
4 the association between *Chlamydia trachomatis* major outer membrane protein (MOMP) peptide-
5 specific IgG antibodies and ectopic pregnancy (EP), miscarriage, and preterm delivery. Cases for EP
6 and miscarriage were identified through the Hospital Discharge Register from 1998-2005 and
7 preterm delivery cases from the Finnish Medical Birth Register from 1988-2005. Controls were
8 matched to cases by sampling time, age at serum sampling, and postal code district. The majority of
9 subjects were aged 20-34. They found no evidence of an association between anti-chlamydial IgG
10 antibody and miscarriage or preterm birth, however 21.0% of EP cases and 14.6% of controls were
11 positive giving an OR in the EP cases versus matched control group of 1.56 (95% CI 1.20-2.03). Whilst
12 this provides good statistical evidence of an association the result is difficult to interpret in terms of
13 population burden of disease caused by CT infection. This paper investigates what this result might
14 mean for the population excess fraction (PEF) of EP due to CT.

15 The PEF is the proportional reduction in disease risk that would be achieved by eliminating the
16 exposure of interest from the population, assuming the exposure is causally related to the disease.²
17 A number of formulae have been derived by which the PEF can be estimated from epidemiological
18 data. The formula giving an estimate from case-control studies is:

19
$$PEF = \frac{\pi \cdot (OR - 1)}{\pi \cdot (OR - 1) + 1}$$

20 Where OR equals the odds of exposure in the diseased (case) group divided by the odds of exposure
21 in the non-diseased (control) group and π is the prevalence of the exposure in the population. The
22 OR is an approximation to the incidence rate ratio and is appropriate if the disease is sufficiently rare
23 (as is the case for EP). The presence of π in the formula reminds us that the PEF has only a “local”
24 interpretation: it is not only a property of the disease and the exposure, but of the time and place
25 where the data were collected. An important caveat is that the formula is only correct if there are no
26 confounding factors or they have all been ‘correctly’ adjusted for.

27 In order to use this formula in the current context it is necessary to specify the prevalence of
28 exposure in the population. This is not straight forward to define, and is even more difficult to
29 estimate. Anti-chlamydial IgG antibody positivity is a proxy measure for current or previous exposure
30 to CT (the cumulative incidence proportion). However, antibody levels often decline over time,
31 sensitivity and specificity levels of antibody tests are imperfect, and may differ between cases and
32 controls.³ Furthermore, cumulative exposure depends on re-infection patterns. So population level
33 estimates of exposure levels are difficult to obtain. In the Finnish study around 15% of controls were
34 anti-chlamydial IgG antibody positivity. A recent study using the Dunedin New Zealand birth cohort
35 found 24% positivity in women aged 26 using a Pgp3 double-antigen sandwich Enzyme Linked
36 Immunosorbent Assay (ELISA) .⁴ A recent study in the UK using the less sensitive (73.8%) Pgp3
37 indirect ELISA assay found positivity rates of around 20-25% in women aged 23-24⁵.

38

39 Based on this information PEFs can be calculated for a range of population exposure levels within
40 which it is difficult to imagine the truth does not lie. The lower bound is chosen to be the antibody
41 prevalence in the matched control group (15%) and sensitivity of results is assessed for exposure
42 levels up-to a maximum level of 35%. Central estimates of PEF vary between about 8% and 16% with
43 lower and upper 95% confidence limits varying between about 3% and 27% (table 1, column 2).

44 The estimates in column 2 assume the observed OR represents a fully causal relationship. However,
45 even if CT does not cause EP we would still expect to see raised odds of exposure in the cases as the
46 risk factors for CT exposure are the same as some of the other causes of pelvic inflammatory disease
47 (PID) (such as other STI's) and hence for EP. So these PEFs should be viewed as upper bounds.

48 Quantification of the level of confounding in the estimated OR is difficult as the study authors had no
49 information on confounding factors. However, a recent paper applying finite mixture model (FMM)
50 techniques to anti-CT IgG antibody level data in cases with tubal factor infertility (TFI) and pregnant
51 controls in the UK found the effects of confounding could lead to an overestimate of PEF of anything
52 up-to 60% in this group⁶. The titre distributions in cases and controls were modelled as a mixture of
53 several component distributions. The causal mechanisms for TFI were attributed to differences
54 between cases and controls in specific components, rather than differences in overall
55 antibody prevalence, reducing the extent to which PEF estimates are vulnerable to
56 confounding. This same adjustment applied to the PEFs calculated above gives central estimates
57 ranging from 5% to 10% with lower and upper confidence limits between 2% and 16% (table 1,
58 column 3). However, this is likely an over-adjustment so these estimates should be regarded as
59 lower bounds .

60 A recent report estimated the PEF of EP due to CT in the UK in the early 2000's to be about 5%.⁷ The
61 UK analysis did not account for the greater than additive effect of multiple PID episodes on EP risk
62 observed in prospective studies which might raise it to around 8%. Different PEFs are not directly
63 comparable as they are time and place specific. However, the EP data from the Rantsi *et al*¹ study
64 cover the period 1998-2005, a similar time frame to the UK work. There is some evidence based on
65 positivity rates in CT tests that population chlamydia exposure may have been higher in Finland than
66 in the UK during this period.⁸ Which may explain why the PEF estimate for Finland is slightly higher
67 than for the UK. However, whilst it is difficult to know, there is likely to be at least a reasonable
68 degree of homogeneity in risk patterns across most of Western Europe, a view supported by the
69 relatively close agreement between these two sets of estimates.

70 Both the UK report and the analysis here suggest that previous estimates of the PEF of EP due to CT
71 of up-to 25%⁹ likely overestimate the importance of CT on the population burden of EP. In the
72 present case, one would have to propose fairly extreme assumptions about exposure prevalence,
73 confounding, and the direction and size of sampling error to obtain a PEF that is even close to this.
74 Overall it seems likely that PEFs of EP due to CT generally lie between around 5% and not much more
75 than 10%. If salpingitis is the only causal pathway through which CT can cause EP this is consistent
76 with recent estimates of the PEF of salpingitis due to CT of around 20%, and the PEF of EP due to
77 salpingitis of around 30% for the same period in the UK.⁷

78 The excellent study by Rantsi *et al*¹ has added valuable new data for understanding the role of CT in
79 the etiology of EP. The analysis here is based upon assumptions about population exposure patterns
80 and confounding. It may be possible to obtain a more robust estimate of PEF for this population

81 through direct application of FMM methods to the raw MOMP absorbance data. Such a
82 methodology avoids the need to estimate population exposure prevalence and mitigates the effect
83 of unmeasured confounding on the estimates⁶.

84

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108

109 Table 1. Estimated unadjusted and adjusted PEFs of EP due to CT (95% Confidence limits) in Finland
 110 for different assumed population exposure proportions.

Assumed proportion of population ever exposed	PEF (95% CI) unadjusted	PEF (95% CI) adjusted*
0.15	7.7% (2.9%,13.4%)	4.6% (1.7%, 8.0%)
0.2	10.1% (3.8%,17.1%)	6.0% (2.3%,10.2%)
0.25	12.3% (4.8%,20.5%)	7.4% (2.9%,12.3%)
0.3	14.4% (5.7%,23.6%)	8.6% (3.4%,14.2%)
0.35	16.4% (6.5%,26.5%)	9.8% (3.9%,15.9%)

111

112 Adjusted PEF assumes the unadjusted PEF overestimates by 60% (see text)⁶