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Title: Time to take causation seriously

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Conflicts of Interest:

PJH reports personal fees from Aquarius Population Health, grants, personal fees and non-financial support from Cepheid, personal fees from Crown Prosecution Service, personal fees from British Association for Sexual Health and HIV, grants from Mast Group Ltd, grants and personal fees from Hologic, outside the submitted work; in addition, PJH has a patent A sialidase spot test to diagnose bacterial vaginosis, issued to University of Bristol. The remaining authors declare no conflicts of interest.

Davies *et al* use data from a cohort of chlamydia tested and never-chlamydia tested women constructed from the Danish registry study to estimate the risk of reproductive complications¹. The analyses show associations between chlamydia testing (positive, negative, untested) and reproductive outcomes over the subsequent 15 years. However, the paper and an accompanying editorial seriously over-interpret the data.

Loose language crosses the line between causation and association. For example, statements like “a positive chlamydia test increased the risk... by at least 30%”, “a single diagnosed infection increases the risk...” or “... a repeat diagnosis increases the risk” strongly imply causality. The design is similar to the earlier Uppsala study². A CDC expert group³ identified a series of methodological difficulties with studies of this type, among them the already insurmountable problem that women testing positive were treated. It is simply not possible to derive meaningful, causal estimates from studies of this type, and the editorialist’s assertion that the paper “quantified the risk of reproductive complications attributable to chlamydia infection” is incorrect.

As the study gives no evidence that the single or repeat events of CT diagnosis (positive or negative) cause an increase in the risk of complications, it cannot substantiate claims that interrupting this will be effective. So although the conclusion that “control programs must prevent first and repeat infections to improve women’s reproductive health” could be correct, this study adds no relevant information to support it, nor to the editorialist’s recommendation of “a more intensive approach than test and treat”.

We recently published estimates of the risks of reproductive damage attributable to chlamydia⁴ in the UK. Central estimates are that every 1,000 CT infections in women on average cause 170 episodes of PID, 70 of salpingitis, 2 ectopic pregnancies (EP) and 5 of Tubal Factor Infertility (TFI). These estimates, which include undiagnosed chlamydia, PID and salpingitis, were based on estimates of chlamydia incidence, prevalence and duration in the UK, an estimate of the risk of PID following CT infection based on randomized evidence, and many other sources of systematically identified evidence. These estimates were constructed in a way that makes them internally coherent and consistent with data on the incidence of PID, EP and TFI in the UK.

Finite mixture modeling of serology data may be another route towards estimating the proportion of reproductive damage attributable to chlamydia⁵, but this needs further validation.

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