Reviewer’s report

**Title:** Association of Circulating Chlamydia pneumoniae DNA with Cardiovascular Disease: A Systematic Review.

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**Reviewer:** Dr M Leinonen

**Level of interest:** A paper of considerable general medical or scientific interest

**Advice on publication:** Accept without revision

**General comments**

The present manuscript "Association of circulating Chlamydia pneumoniae DNA with cardiovascular disease. A systematic review" by Smieja et al. is very timely and an important contribution to the field of chlamydia research. Several laboratories have recently analyzed the presence of C. pneumoniae DNA both in respiratory specimens, atherosclerotic lesions and circulating white blood cells using variable, nonstandardized PCR methods and on the basis of the results obtained, claimed that C. pneumoniae is either associated or not associated to different diseases. In the present article, the authors sought the studies in which C. pneumoniae DNA had been looked for in peripheral blood mononuclear cells of patients with cardiovascular diseases and in nondiseased controls and used a meta-regression analysis to find epidemiological and methodological factors associated to high prevalence of positive findings. The article covers very well the published data (articles and abstracts) on this field. The results show that e.g. DNA extraction method, sample volume and used amplification target affect the numbers of positive findings. In addition, smoking and season seem to have effect on the positivity rate. Interestingly, smoking is an important risk factor for cardiovascular diseases and several studies have also demonstrated the elevated morbidity and mortality of cardiovascular diseases during winter months. Thus, we can also speculate, if the effects of smoking and season on cardiovascular diseases are actually associated with C. pneumoniae infection.

The authors claim in their article that chlamydial serology is a poor predictor of future cardiac events in prospective studies. In cross-sectional studies, C. pneumoniae antibodies and especially IgA antibodies have, in several studies, been shown to be more common in the patients than in controls. On the other hand, it would also be interesting to see the corresponding meta-analysis of serological studies, showing methodological (e.g. used method: MIF, EIA; experienced vs. nonexperienced laboratory) and epidemiological factors associated to the highest risk for cardiac events.
The paper deserves to be published: it provides useful hints for those laboratories starting this type of studies and helps the readers in assessing the scientific value of published articles on the field.

**Competing interests:**

None declared.