



## ***Letter to the Editor***

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### **Response to Letter to the Editor, re: Ijaz S, et al. “Night-shift work and breast cancer - a systematic review and meta-analysis”**

by [Ijaz S](#), [Verbeek J](#), [Seidler A](#), [Lindbohm M-L](#), [Ojajärvi A](#), [Orsini N](#), [Costa G](#), [Neuvonen K](#)

**Affiliation:** Cochrane Occupational Safety and Health Review Group, Finnish Institute of Occupational Health, Kuopio, Finland. [sharea.ijaz@ttl.fi](mailto:sharea.ijaz@ttl.fi)

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## Response to Letter to the Editor, re: Ijaz S, et al. “Night-shift work and breast cancer – a systematic review and meta-analysis”

We thank Dr Stevens et al (1) for their comments and interest in our work. We also thank the primary study authors who wrote this letter for their contribution and assistance during the course of our review in 2012. We would not have been able to achieve the quality in our analysis without their input. We certainly agree with their opinion on the current state of evidence being less than ideal and needing more rigor. Thus we believe that their arguments support our conclusion that, based on the low quality of exposure data and the difference in effect by study design, our findings indicate insufficient evidence for a causal relationship between night-shift work and breast cancer.

We used recommended guidelines for systematic reviews employing state-of-the-art, valid methods (2–4). One of the key features is that studies of sufficient clinical and statistical homogeneity are combined (5). Clearly the studies that did not fit our predefined criteria for night-shift work based on Stevens et al (6) were not included in the meta-analysis and conclusions. Variation in exposure definition and assessment was further taken into account in risk of bias assessment and did not change results in a subsequent sensitivity analysis. Further bias in our review was avoided by ensuring all decisions on the handling of data were made in advance (a priori protocol) thus separating tested prior hypotheses from ones generated by the data (post hoc). We formulated clear hypotheses about the association between exposure to shift work and breast cancer, which we tested as far as possible given the limitations of the data in the primary studies. We agree that misclassification of exposure is possibly at work in these studies but this would not always be non-differential. Even when this is the case, it is not easy to predict the final result of this bias when the exposure is not dichotomous, as is the case with shift work (7).

In the absence of real evidence, we are not convinced that recall bias can be ruled out completely from case-control studies except when the exposure was measured objectively in advance of disease occurrence. Evidence exists that systematic bias occurs in peoples' reporting of their shift-work experience (8). Most areas of medicine today follow the hierarchy of evidence, preferring prospectively followed-up data to assert or refute causal relationships (9–11), and it should be the same here.

We do not know if a long-term risk exists or not because, until Grundy et al's (12) recently published findings, studies have not used an evidence-based a-priori classification of exposure time but rather a data-driven approach to analysis. Following the Grundy et al study, apparently long-term has been defined as >30 years of exposure; we recommend this be further explored.

As Stevens et al (1) point out, other meta-analyses came to different conclusions. This is the result of using different inclusion criteria, different methods for combining studies, and the risk of bias assessment. Per GRADE's (13) recommendation, we used a systematic approach in grading the quality of the evidence. As a result, we rated the evidence as being of very low quality, which means we have little confidence in the results. The authors are also correct in saying that more primary studies find a positive than a negative link. However this method of evidence synthesis, also called vote counting, is widely known to lead to incorrect conclusions.

Repeating more meta-analyses and primary studies is not going to bring us closer to the truth, unless the issues in previous research are redressed by improved methods in the future, guidelines for most of which exist in the literature.

To this end, a research group recently proposed the idea of conducting an individual participant data (IPD) meta-analysis using the available primary studies. We welcome this initiative as it can put to rest some doubts and save valuable resources. An alternative could be to pool/connect all databases that contain information on working hours and analyze these together as a large single study for hypotheses defined a-priori.

We believe that both shift-work exposure and breast cancer are important public health issues that deserve better studies to underpin decisions on causes and solutions.

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Sharea Ijaz,<sup>1</sup> Jos Verbeek, Andreas Seidler, Marja-Liisa Lindbohm, Anneli Ojajarvi, Nicola Orsini, Giovanni Costa, Kaisa Neuvonen

<sup>1</sup> Cochrane Occupational Safety and Health Review Group, Finnish Institute of Occupational Health, Kuopio, Finland [e-mail: [sharea.ijaz@ttl.fi](mailto:sharea.ijaz@ttl.fi)]