

Letter

Indication bias or protopathic bias?

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In their article, Daniels and colleagues describe how the association between NSAID use and spontaneous abortions can be biased by the fact that NSAIDs could be taken to relieve the pain due to early symptoms of the spontaneous abortion itself [1]. The term 'indication bias' is used to define this bias but many readers may have been surprised not to find the term 'protopathic bias'.

In the pharmacoepidemiology book edited by Brian L. Strom, the definition for indication bias (also referred as confounding by indication) states that it 'occurs when the risk of an adverse event is related to the indication for medication use but not the use of the medication itself' [2]. In other words, confounding by indication appears when the reason of prescription is associated with the outcome of interest. On the other side, the definition for the protopathic bias (also called 'reverse causality') refers to the one by Alvan R. Feinstein. Protopathic bias may occur 'if a particular manoeuvre was started, stopped or otherwise changed because of the baseline manifestation caused by a disease or other outcome event' [3]. Therefore, in pharmacoepidemiology, the protopathic bias occurs when the drug is initiated in response to the first symptoms of the disease which is, at this point, undiagnosed. The bias described by Daniels and colleagues in their study matches perfectly with this category of bias and some authors consider that, in such situation, the use of the term 'confounding by indication' is incorrect [4]. Confounding by indication and protopathic bias seem similar but are not synonymous (although sometimes it may be difficult to distinguish between the two).

In the study by Daniels and colleagues, the use of the term 'protopathic bias' may have been more appropriate also because this bias has a specificity. It can be controlled by adding a lag time into the exposure *i.e.* excluding the exposure in a time period before the occurrence of the

outcome [5]. That is what has been done in the study by Daniels and colleagues when exposures to NSAIDs that occurred on the days immediately before the abortion were excluded, and that is how the effect of the bias has been demonstrated.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous three years and no other relationships or activities that could appear to have influenced the submitted work.

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