Editorial

Causal inference and evidence-based recommendations in occupational health and safety research
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This article in PubMed: www.ncbi.nlm.nih.gov/pubmed/33005958

Causal inference and evidence-based recommendations in occupational health and safety research

In this issue of the Journal, a group of distinguished Nordic researchers, led by Anne Helene Garde and including four of our Associated Editors, present a discussion paper that originated from a workshop and provides detailed recommendations on night shift work (1). The recommendations are very clear: to protect workers' health, night shift schedules should have: (i) ≤3 consecutive night shifts; (ii) shift intervals of ≥11 hours; and (iii) ≤9 hours shift duration. For pregnant women, night work should be limited to one shift per week. The authors acknowledge that under circumstances allowing better possibilities for daytime sleep, recommendations could be different.

The discussion paper is remarkable in that it provides clear and strong recommendations based on what the authors themselves call a "limited literature", thus a limited scientific evidence on the risk of shift work for cancer and other health and safety risks. In a recent editorial, British researchers concluded that, due to heterogeneity of shift working in longitudinal studies, it is too difficult to draw a firm conclusion about the risk of breast cancer, let alone about an exposure threshold for night shift work (2). Yet, both Nordic and British researchers seemed to agree that we should not postpone recommendations on best practice in shift work scheduling for reasons of lack of certainty on causal inference.

For the most important health and safety conditions the Nordic authors are concerned with – cancer, cardiovascular disease, diabetes, injuries and pregnancy-related outcomes – the evidence relies on observational studies. Although longitudinal studies on shift work increasingly use register-based exposure information on working hours patterns, often based on payroll data that is linked with registers in healthcare (3, 4), these studies are still vulnerable to important biases, such as selection bias and residual confounding. There are several examples in the literature of well-conducted observational studies suggesting an effect of an exposure that subsequently was not corroborated in randomized controlled trials (RCT). One of the most famous examples is hormone replacement therapy (HRT) in post-menopausal women. Numerous observational studies suggested a protected effect of HRT with regard to risk of cardiovascular disease (5, 6), but when an RCT was finally conducted, it found the effect of HRT to be more harmful than beneficial (7). Recently, a large-scale RCT found no effect of vitamin D intake on reduced risk of depression (8), despite numerous observational studies suggesting such an effect (9). Thus, there are good reasons to treat results from observational studies with caution.

On the other hand, exercising caution does not mean that one should abstain from making recommendations when evidence is based on observational studies only, in the hope that this would keep one on the safe side of scientific scrutiny. There is no safe side. In accordance with Paul Watzlawick's famous quote that "one cannot not communicate" (10), it can be reasoned that not making recommendations is also a form of recommendation, the recommendation to continue business as usual. The recommendation to stop asbestos production, which rather came too late than too early, was not based on RCT but observational studies on the multiple health-hazardous effects of asbestos (11). Thus, when considering the evidence, researchers should not only consider the best evidence based on available data and their causal inference, but also the potential consequences of continuing current practice.

Fifty-five years ago, Sir Austin Bradford Hill published his famous nine viewpoints on causal inference in health research (12). As pointed out by Bradford Hill, as well as other scholars (13), none of the nine viewpoints (today mostly known as "criteria") ensures that an observed observation is causal, however, they still might be helpful in assessing the confidence whether or not a measure of association indicates a causal link between two variables. Today, causal inference remains an intensively discussed topic. In its December 2016 issue, the *International Journal of Epidemiology* published a series of articles, discussion papers and letters on causal inference in epidemiology, in particular on the merits and limitations of the counterfactual "potential outcome approach",

which relies heavily on experiments whether induced by the researcher or natural changes in particular situations that may be interpreted as happening at random (14, 15). This approach has been criticized by proponents of a more "pluralistic approach" for a variety of reasons, among others that it limits causality to particular factors that are usually not widely generalizable (16, 17). Very recently (September 2020), in an opinion paper (18), the main proponent of the potential outcome approach, Tyler VanderWeele asked: "Can sophisticated study designs with regression analyses of observational data provide causal inferences?" The answer seem to be a cautious "yes". Regarding single observational studies, VanderWeele lists eight considerations that increase confidence in the estimate, including longitudinal design; the quality of the assessment of exposure, outcome and confounders; flexible statistical modeling examining robustness to modelling decisions; and attempts to address unmeasured confounding. Evidence then may evolve from accumulation of results from multiple high-quality studies, in particular if these have different designs that are subject to different biases (18).

The struggle on causal interpretation and subsequent evidence-based recommendations is also visible in the GRADE (Grading of Recommendations, Assessments and Evaluations) system, which rates the certainty of evidence and the strengths of recommendations in systematic reviews, for example in *Scandinavian Journal of Work, Environment and Health* articles (19-22). As GRADE has its origins in healthcare evaluation, its evidence assessment favors the RCT, and although the GRADE working group encourages applying GRADE to observational studies (23), the quality rating of observational studies always starts with "low quality", with possibilities for upgrading and downgrading, whereas the quality rating of RCT starts with "high quality". The recently developed "Navigation Guide" (24) - a methodology for synthesizing evidence in systematic reviews that evolved from environmental research but is now also applied in occupational health research (25, 26) - recommends a different approach, where the quality assessment of observational studies starts with "moderate" before the process of up- or downgrading (24).

The paper by Garde et al (1) is not a systematic review, it uses neither GRADE nor Navigation Guide methodology and does not grade the evidence. It is a discussion paper written by leading researchers in the field that base their conclusions and recommendations on their knowledge of the literature, including systematic reviews. Given that a substantial proportion of the workforce is exposed to some type of night shift work, this is a bold, but necessary, step. We are looking forward to further research, both original studies and reviews, corroborating or challenging the conclusions and recommendations of this discussion paper.

References

1. Garde AH, Begtrup L, Bjorvatn B, Bonde JP, Hansen J, Hansen ÅM, et al. How to schedule night shift work in order to reduce health and safety risks. Scand J Work Environ Health. 2020;46(6):557–569. https://doi.org/10.5271/sjweh.3920

2. McElvenny DM, Crawford JO, Cherrie JW. What should we tell shift workers to do to reduce their cancer risk? Occup Med (Lond). 2018;68(1):5-7. https://doi.org/10.1093/occmed/kqx187

3. Nielsen HB, Larsen AD, Dyreborg J, Hansen ÅM, Pompeii LA, Conway SH, et al. Risk of injury after evening and night work - findings from the Danish Working Hour Database. Scand J Work Environ Health. 2018;44(4):385-393. https://doi.org/10.5271/sjweh.3737

4. Härmä M, Ropponen A, Hakola T, Koskinen A, Vanttola P, Puttonen S, et al. Developing register-based measures for assessment of working time patterns for epidemiologic studies. Scand J Work Environ Health. 2015;41(3):268-279. https://doi.org/10.5271/sjweh.3492

5. Grodstein F, Stampfer M. The epidemiology of coronary heart disease and estrogen replacement in postmenopausal women. Prog Cardiovasc Dis. 1995;38(3):199-210. https://doi.org/10.1016/S0033-0620(95)80012-3

6. Grodstein F, Stampfer MJ, Manson JE, Colditz GA, Willett WC, Rosner B, et al. Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. N Engl J Med. 1996;335(7):453-461. https://doi.org/10.1056/NEJM199608153350701

7. Manson JE, Hsia J, Johnson KC, Rossouw JE, Assaf AR, Lasser NL, et al. Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med. 2003;349(6):523-534. https://doi.org/10.1056/NEJMoa030808

8. Okereke OI, Reynolds CF, 3rd, Mischoulon D, Chang G, Vyas CM, Cook NR, et al. Effect of long-term vitamin D3 supplementation vs placebo on risk of depression or clinically relevant depressive symptoms and on change in mood scores: a randomized clinical trial. JAMA. 2020;324(5):471-480. https://doi.org/10.1001/jama.2020.10224

9. Li H, Sun D, Wang A, Pan H, Feng W, Ng CH, et al. Serum 25-hydroxyvitamin D levels and depression in older adults: a dose-response meta-analysis of prospective cohort studies. Am J Geriatr Psychiatry. 2019;27(11):1192-1202. https://doi.org/10.1016/j.jagp.2019.05.022

10. Watzlawick P, Beavin-Bavelas J, Jackson D. Pragmatics of human communication. A study of interactional patterns, pathologies and paradoxes. New York: Norten; 1967.

11. Gee D, Greenberg M. Asbestos: from 'magic' to malevolent mineral. In: European Environment Agency, editor. Late lessons from early warnings: the precautionary principle 1896-2000. Environmental issue report No 22/2001. Luxembourg: Office for Official Publications of the European Communities; 2001. p.52-63. Available from: https://www.eea.europa.eu/publications/environmental_issue_report_2001_22.

12. Bradford Hill A. The environment and disease: association or causation? Proc R Soc Med. 1965;58:295-300. https://doi.org/10.1177/003591576505800503

13. Rothman KJ, Greenland S. Causation and causal inference in epidemiology. Am J Public Health. 2005;95 (Suppl 1):S144-150. https://doi.org/10.2105/AJPH.2004.059204

14. VanderWeele TJ. Commentary: On causes, causal inference, and potential outcomes. Int J Epidemiol. 2016;45(6):1809-1816.

15. Robins JM, Weissman MB. Commentary: Counterfactual causation and streetlamps: what is to be done? Int J Epidemiol. 2016;45(6):1830-1835.

16. Vandenbroucke JP, Broadbent A, Pearce N. Causality and causal inference in epidemiology: the need for a pluralistic approach. Int J Epidemiol. 2016;45(6):1776-1786. https://doi.org/10.1093/ije/dyv341

17. Krieger N, Davey Smith G. The tale wagged by the DAG: broadening the scope of causal inference and explanation for epidemiology. Int J Epidemiol. 2016;45(6):1787-1808. https://doi.org/10.1093/ije/dyw114

18. VanderWeele TJ. Can sophisticated study designs with regression analyses of observational data provide causal inferences? JAMA Psychiatry. Online First https://doi.org/10.1001/jamapsychiatry.2020.2588

19. Rönnblad T, Grönholm E, Jonsson J, Koranyi I, Orellana C, Kreshpaj B, et al. Precarious employment and mental health: a systematic review and meta-analysis of longitudinal studies. Scand J Work Environ Health. 2019;45(5):429-443. https://doi.org/10.5271/sjweh.3797

20. Andersen JH, Malmros P, Ebbehoej NE, Flachs EM, Bengtsen E, Bonde JP. Systematic literature review on the effects of occupational safety and health (OSH) interventions at the workplace. Scand J Work Environ Health. 2019;45(2):103-113. https://doi.org/10.5271/sjweh.3775

21. Oakman J, Neupane S, Proper KI, Kinsman N, Nygard CH. Workplace interventions to improve work ability: A systematic review and meta-analysis of their effectiveness. Scand J Work Environ Health. 2018;44(2):134-146. https://doi.org/10.5271/sjweh.3685

22. Stock SR, Nicolakakis N, Vezina N, Vezina M, Gilbert L, Turcot A, et al. Are work organization interventions effective in preventing or reducing work-related musculoskeletal disorders? A systematic review of the literature. Scand J Work Environ Health. 2018;44(2):113-133. https://doi.org/10.5271/sjweh.3696

23. Schünemann H, Hill S, Guyatt G, Akl EA, Ahmed F. The GRADE approach and Bradford Hill's criteria for causation. J Epidemiol Community Health. 2011;65(5):392-395. https://doi.org/10.1136/jech.2010.119933

24. Woodruff TJ, Sutton P. The Navigation Guide systematic review methodology: a rigorous and transparent method for translating environmental health science into better health outcomes. Environ Health Perspect. 2014;122(10):1007-1014. https://doi.org/10.1289/ehp.1307175

25. Li J, Pega F, Ujita Y, Brisson C, Clays E, Descatha A, et al. The effect of exposure to long working hours on ischaemic heart disease: A systematic review and meta-analysis from the WHO/ILO Joint Estimates of the Work-related Burden of Disease and Injury. Environ Int. 2020;142:105739. https://doi.org/10.1016/j.envint.2020.105739

26. Descatha A, Sembajwe G, Pega F, Ujita Y, Baer M, Boccuni F, et al. The effect of exposure to long working hours on stroke: A systematic review and meta-analysis from the WHO/ILO Joint Estimates of the Work-related Burden of Disease and Injury. Environ Int. 2020;142:105746. https://doi.org/10.1016/j.envint.2020.105746

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