that researchers are aware of the wide range of models available, and choose the model(s) appropriate for their particular research question, mindful that there are instances when interpretation might be challenging.

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References

More ways to distinguish real from artefactual associations in observational studies

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We read with interest the study by Bergmann et al. on the association of the pattern of lifetime alcohol use with causes of death.1 The different techniques used, such as negative controls, classification of former users and examination of consistency across subgroups, are crucial as they help to identify any potential biases, which may not be adequately corrected for by conventional statistical adjustment. In addition to the ‘intention to treat’ approach suggested in the commentary,2 we would like to suggest two alternative, complementary approaches which may also help distinguish whether associations are real or artefactual.

First, use could be made of a setting with less confounding of the association in question, where in any unbiased study design a null association would be expected if the associations in other settings were due to confounding, perhaps using a cross cohort comparison3 or a comparison of other study types across settings. For example, the pattern of alcohol use in China is different from that in the West. Specifically, in the West moderate users have a wide range of healthier attributes compared with never users,4 but not so much in China.5 Given the different confounding between moderate alcohol use and cardiovascular diseases in these different settings, any discrepant findings between these settings may suggest confounded contextually specific associations rather than biologically based relations. Comparing associations across contexts has been exploited successfully previously for other exposures, such as breastfeeding,1 where experiments are difficult to conduct. Notably, the associations of breastfeeding with health outcomes in Hong Kong, where breastfeeding has little clear social patterning, are similar to those found in a randomized controlled trial of breastfeeding promotion, but different from those usually observed in the West where breastfeeding and most health outcomes are strongly associated with socio-economic position.6,7 Recent expansion of epidemiological studies to understudied non-Western populations with different patterns of confounding may provide a range of potential settings to facilitate such investigations. However, researchers might need to be encouraged to publish findings from such settings, that challenge received wisdom, because they may be perceived as ‘wrong’ at first glance and overlooked in favour of other findings that are easier to publish.

Second, Mendelian randomization, that is instrumental variable analysis with genetic instruments,8 could be used. Mendelian randomization analyses involve the use of genetic instruments, for example alcohol processing genes as an instrument for alcohol use,9 and are generally less susceptible to confounding and selection bias, provided the corresponding assumptions are fulfilled. Again, this approach has been used successfully elsewhere, for example to assess

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the causal role of risk factors in cardiovascular diseases, such as the (lack of) effect of C-reactive protein on ischaemic heart disease.\textsuperscript{10}

Observational studies are vulnerable to bias and confounding and the results from them should be interpreted with caution, as Bergmann \textit{et al.} stated.\textsuperscript{1} The approaches used by Bergmann \textit{et al.},\textsuperscript{1} advocated in the commentary,\textsuperscript{2} and those suggested in this letter could all be exploited more often when trying to establish the effects of any exposure on health from observational data, to improve causal inference, with corresponding implications for the formulation of public health policy.

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\section*{References}


