Potential biases when observing increased mortality risk in association with smoking cessation among older adults

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Key points:

- Observational associations between smoking cessation and mortality among older adults should be interpreted with caution
- Unmeasured confounding is one potential bias
- Collider bias related to survival may also be an issue

The paper by Yuan Wei et al. appears to show that smoking cessation in later life increases rather than decreases mortality risk [9]. This is counter to prevailing thinking regarding effects of smoking and smoking cessation on health. Plausible biological mechanisms to account for this surprising finding can be postulated, but we must also consider alternatives to a causal interpretation for this association.

A useful approach to causal inference from observational data is to compare and contrast the observational study with a hypothetical 'target' randomised trial that, ethics and practicality aside, might have been conducted to study the effect of interest [1]. In this case, interest is in the effects of smoking history (including persistent smoking and different patterns of cessation) on mortality among people aged 80 and over. A hypothetical trial might have recruited a group of smokers and randomised them to either smoking cessation, or continued smoking, and then compared mortality risk between the two groups over some years of follow-up. The hazard ratios presented by Yuan Wei et al. for smoking cessation compared smokers who quit with never smokers, rather than against current smokers. While the hazard ratios for two of the three smoking cessation groups (transient and recent quitters) were considerably larger than those comparing current to never smokers, the actual magnitude of the risk differences for smoking cessation in comparison to persistent smoking are smaller than the hazard ratios presented, and the magnitude of risk can be important when considering potential biases.

Now let us consider some potential sources of bias. Causal inference relies on exchangeability, that comparison groups have similar mortality risk other than due to the effect of the exposure [2]. In a randomised trial this would be achieved by randomising participants to either persistent smoking or

cessation, but in an observational study allocation is non-random. Causal interpretation of the observational association requires the assumption that adjustment for confounders was sufficient to account for non-random differences between the comparison groups. A good range of confounders were adjusted for, including sociodemographic, health behaviour, and health variables. The authors particularly explored the notion of 'sick quitters', i.e. that poor health could prompt smoking cessation and confound the relationship with mortality. A range of sensitivity analyses were conducted to assess this, with findings appearing robust to this sort of explanation. Nevertheless, there could still be unobserved confounders (especially residual unmeasured differences in health) that affect both the likelihood of cessation and mortality. The magnitude of risk is important here, because only a small degree of unmeasured confounding is needed to account for small magnitude risk differences [3].

Potential bias from unmeasured confounding is common to most observational studies, but another potential source of bias more specific to this study, is that participants had to have survived to reach age 80 or more at the time of the baseline survey. Imagine a trial that randomised participants early in life to either persistent smoking or smoking cessation at different ages. If this trial only assessed outcomes among those who survived to age 80 then it could produce biased findings. Assume that smoking increases risk for mortality before age 80, and that smoking cessation reduces this risk, which is plausible given existing data [4-7]. Persistent smokers would be less likely to survive into the assessment group and those that did would therefore be more likely than those in the comparison groups to have other characteristics determining longevity. Thus, by conditioning on survival to age 80, any unobserved determinant of mortality that is relevant both before and after aged 80 could induce bias in smoking history comparisons (even if participants had been randomised to different smoking histories) [8]. Unobserved factors would only need to determine mortality (before and after age 80) to induce bias in this way and would not also need to be determinants of smoking history, as they would for traditional confounding. This can be called 'collider bias' or 'selection bias', and it can occur when conditioning on an outcome (like survival) that is causally influenced by the exposure of interest and another unmeasured variable. This is not so much about 'sick quitters', but that the sample is limited (by means of survival) to the healthiest persistent smokers.

Mortality risk is known to continue decreasing with increasing time since cessation, taking several years to approach a level of risk similar to never smokers [5, 7]. If current smokers were the reference group then *a priori*, one would expect hazard ratios for groups with longer periods of cessation to be more severely affected by collider bias, as the longer-term quitters would differ more from current smokers in terms of survival into the sample. However, with never smokers as the reference group, you would expect the hazard ratios to be most biased for current smokers and less so for longer-term quitters (because current smokers and shorter-term quitters would differ most from never smokers in terms of survival). Thus, the hazard ratio for current smoking (which the quitter hazard ratios are compared with) may be the most severely biased of those reported in this study. Regardless of reference group, it is difficult to determine how much of any hazard ratio is due to collider bias, and how much is due to any actual effects of cessation.

A more appropriate randomised trial might recruit older adults who smoke, randomise them to cessation, and then assess mortality risk over follow-up from the point of cessation. By analogy, an observational study would also be less likely to be biased if it compared quitters against comparable smokers with mortality risk assessed over follow-up from the point of cessation, rather than over a period beginning some time after cessation. There have never been randomised trials of the effects of smoking cessation. Sometimes observational data are all we have. But the interpretation of associations is always uncertain, and we should be cautious in drawing conclusions about what can be implemented in health policy.

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