Reverse causality in cardiovascular epidemiological research: more common than imagined?

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It is now well established that observational studies seeking evidence that a risk factor causes a disease are susceptible to various biases. Amongst the most important are residual confounding - whereby unmeasured or imprecisely measured confounders prevent causal inferences being drawn from associations between any two parameters - and reverse causality. Whilst the former is typically acknowledged in reports of such studies, the latter concept appears to be less well understood and therefore may be more often overlooked as a potential explanation for apparent, often unexpected, associations between risk factors and adverse outcomes.

With the potential for reverse causality in mind, Ravindrarajah and colleagues[1] sought to determine whether the association of lower systolic blood pressure (SBP) values with higher mortality in observational studies in the elderly (>75-80 years of age) could be afflicted by this same phenomenon. They did so since recent trial data, in particular the Systolic Blood PRessure INtervention Trial (SPRINT),[2] demonstrated that lowering SBP to a target of less than 120mmHg led to a 33% reduction in all-cause mortality in those above 75 years of age, findings in almost complete contrast with such observational data. To test their hypotheses the authors analyzed data from the Clinical Practice Research Datalink (CPRD), a primary care cohort collected in the UK which, importantly, includes serial measurements of many risk factors. Using this resource they not only addressed association between SBP and mortality but they did so according to (i) frailty category (ii) anti-hypertensive treatment. More importantly, they also asked whether SBP levels declined prior to death and if so how did this decline compare to the pattern of SBP in those who survived, and whether these patterns differed in those on or off blood pressure lowering treatments.

The researchers were able to confirm that men and women aged over 80 and with SBP levels <120mmHg did indeed have higher risks of mortality compared to those with SBP in the range of 120-139mmHg. This J-curve phenomenon has been shown in many previous epidemiological studies, which has raised concerns about the safety of intensive BP lowering in the elderly population. Interestingly, this association was clearly observed across all categories of frailty. This latter finding, they note, is somewhat at odds with prior findings in NHANES[3] where associations of low SBP with mortality were most evident in frailer subjects, a finding somewhat supportive of reverse causality. That said, different frailty indices (which appear complex in their computation) were used in each case and could have led to differential findings and so these frailty-associated differences need to be considered with a degree of caution.

More importantly, by exploiting their access to serial SBP measurements the authors were able to demonstrate a greater decline in SBP in the five years prior to death than was observed in those who remained alive, with a particularly marked decline in the two years before death. This pattern was the same whether or not patients were taking anti-hypertensive medications allowing the researchers to argue that their findings demonstrate an innate (i.e. non-pharmacological) accelerated terminal decline in SBP as individuals approach death, a pattern which would

confound the relevant observational studies which have cast doubt on the safety and efficacy of blood pressure lowering in the elderly. Consequently, the authors conclude that randomized evidence rather than observational data should inform clinical guidelines in this area. We strongly agree. That SBP declines more rapidly in those individuals closer to dying means this is a clear case where reverse causality in observational data (i.e. a pre-morbid condition altering a risk factor, rather than the reverse) can prompt incorrect assumptions about the direction of causation.

Why BP falls to such an extent in those about to die requires further study but falling weight could certainly be a factor. In addition, as the authors point out, systemic inflammation (common in many chronic diseases e.g. heart failure, cancers, renal disease, autoimmune conditions) is often linked to deteriorating nutritional status (i.e. lower caloric intake) towards the end of life and could directly or indirectly contribute to both weight loss and declines in BP.

Interestingly, the notion that poor health conditions leading to low blood pressure could explain the J-shaped association of both SBP and DBP levels with adverse outcomes was proposed more than a decade ago by Boutitie and colleagues[4]. Low levels of both SBP and DBP were noted by these authors to be related to risk for cardiovascular and, informatively, also non-cardiovascular outcomes in the control groups of blood pressure trials; such associations could therefore not be due to anti-hypertensive treatment.

Taking a wider context, these new BP findings of reverse causality should serve as an alert to researchers seeking causal inferences from observational studies. Reverse causality is more often in play than one might imagine. Take for example the issue of sedentary activity or sitting time, an area given plentiful prominence in recent years as a 'cause' of adverse cardiometabolic outcomes.[5] Illness will lead individuals to sit down more often (due to tiredness and fatigue) and watch more television than they would have when their health was better. This means that studies simply investigating the association between sedentary activity and adverse outcomes but not excluding all those with known ill health at baseline may substantially overestimate the importance of sedentary activity to adverse outcomes. This point was appreciated by Ekelund and colleagues[6] in their recent relevant meta-analysis which concluded that 'high levels of moderate intensity physical activity (ie, about 60–75 min per day) seem to eliminate the increased risk of death associated with high sitting time'[6]. In this meta-analysis, to lessen chances of reverse causality the authors chose studies which either excluded individuals who had ill health from some (though not all) important causes at baseline or studies which excluded deaths occurring in the first one or two years of follow-up. Even with perfect cataloguing of risk factors and concomitant illnesses, however, the influence of reverse causality cannot be entirely removed, partly due to the presence of sub-clinical illness.

The issue of sub-clinical disease is relevant to many areas of epidemiological research including

sedentary activity and other lifestyle behaviors, for example: adiposity (weight can fall or change its trajectory well before any clinical diagnosis of ill health and, in some cases, many years before death); intake of alcohol (a well-known phenomenon of 'sick quitters' whereby ill health leads individuals to curtail or stop drinking alcohol); and physical activity levels per se (ill people have less energy to expend). Observational studies, however large, cannot offer definitive conclusions regarding cause and effect particularly when issues of reverse causality can influence multiple key exposures, thereby potentially exaggerating the strengths of associations. Trials testing change in sedentary behavior are ongoing, albeit based on surrogate cardiovascular outcomes, and these should better inform relevant guidelines although the general message to be more physically active is of course entirely justifiable based on other stronger data, including some trials.

There are many other pertinent examples whereby reverse causality can muddy findings in cardiovascular research (see Table 1 for specific examples).

Table1. Examples of risk factors or health behaviors which can be influenced by reverse causality

Risk parameters	Observational findings	Evidence for such associations being affected by reverse causality
BP	• Low SBP and DBP associated with greater mortality in elderly	• Serial data show SBP declines in an accelerated fashion in people destined to die versus those who survive, with marked fall in 2 years prior to death[1] • Randomized trial showed mortality benefits of lowering SBP to <120mmg Hg in individuals over 75 years of age[2]
BMI	• Low BMI in many observational and chronic disease (e.g. heart failure, renal disease, rheumatoid arthritis) cohorts associated with greater mortality risks	• Serial data reveal BMI declines in advance of death in many conditions (e.g. rheumatoid arthritis, chronic heart failure) • Genetic epidemiology shows higher mortality risks with higher BMI • Epidemiological associations between BMI and mortality stronger in younger age groups in whom reverse causality will be less[7]
Cholesterol	• Low cholesterol associated with higher cancer risk	• Serial data reveal cholesterol declines in advance of cancer diagnosis[8] • Randomized trials of statins show no increase in cancer risk[9] • Genetic epidemiology shows those with lower cholesterol do not have higher cancer rates[8]
HbA1c	• Low HbA1c associated with higher mortality risks in diabetes cohort[10]	• Similar findings also seen in patients without diabetes, suggesting that findings are not necessarily related to glucose-lowering therapy[11] • Recognition that glucose levels can decline with some chronic illnesses e.g. renal disease and with unintentional weight loss • Genetic epidemiology predicts higher CVD and mortality risks with higher glucose[12]
Vitamin D	• Low vitamin linked to adverse outcomes in many diseases[13]	• Ill people go outside less often so are less exposed to sunlight[14] • Vitamin D is an acute phase reactant and declines with the inflammatory cytokine rise in acute and chronic diseases[14] • No evidence from randomized trials that vitamin D supplementation lessens mortality risks in such conditions
Alcohol intake	• Non-drinkers are at higher risks of CVD compared to moderate drinkers	• Genetically associated lower alcohol intake is associated with lower, not higher, CVD, BP and weight[15]

Notably, the observational association of low cholesterol levels with higher cancer risk has been shown to not be causal in statin trials which show no increase in cancer rates.[9] Furthermore, by using serial trial data, we demonstrated cholesterol levels decline well before diagnosis of cancer

is made,[8] a finding in line with reverse causality and potentially due to systemic inflammation in cancers driving down circulating cholesterol levels.

These observations lead one to ask what statistical methods beyond serial tracking of data could help uncover reverse causality or else attenuate its influence in data analyses. There is no one definitive method but rather a series of approaches, all dependent on availability of different types of data, are often needed. The recent Global BMI mortality collaboration provides one of the best examples in the controversial adiposity area.[7] This latter study concluded that both overweight and obesity were associated with higher all-cause mortality. To limit reverse causality in this paper, the authors took several steps: (i) they examined the data only for never-smokers (given smoking lowers weight yet increases mortality), (ii) they removed those with chronic diseases (as far as pragmatically possible) and, (iii) they excluded all deaths in the first five years of follow up. In addition, they looked at the associations between BMI and mortality within differing age groups and were able to demonstrate a stronger association in younger age groups. This latter finding is important since the youngest group is least likely to be afflicted by reverse causality and thus associations of adiposity with mortality in the younger groups provide more confidence in a causal relationship.

Finally, the emerging area of genetics could help further uncover reverse causality since any common polymorphisms which mark life-long differences in risk factors (without influencing other pathways) can be used as instruments of life-long exposure to such risk factors. Returning to the example of cholesterol and cancer, in the same report in which we showed that cholesterol levels fall before cancer diagnosis, we also demonstrated that those with genetically lower cholesterol levels did not have higher cancer outcomes[8] replicating the robust results pooled from the statin trials[9]. Similarly, other genetic data support causal links between obesity and higher mortality, as well as between other commonly measured risk factors (lipids, glycemia)[16,12] and cardiovascular events. Genetic studies have also challenged the long assumed protective effect of alcohol on cardiovascular disease.[15] However, while such genetics studies can overcome many of the limitations inherent in observational studies which seek evidence of causal relationships between risk factor and disease, this type of work is itself not completely without potential bias and so should not be considered in isolation.

In summary, the study by Ravindrarajah and colleagues is a timely reminder that many potential biases including, but not limited to, reverse causality should be borne in mind in epidemiological analyses which seek to make causal inferences.

Disclosures:

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