

COMMENTARY

Nutrition and venous thrombosis: An exercise in thinking about survivor bias

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Suppose you listen to a radio station that usually plays contemporary music hits, but has a “listener request hour” for classic songs. At the end of the hour the DJ sighs that, “they don’t make songs like they used too.” However, as the DJ did not play or recall all the other songs that were produced around the time that the classic song was produced, how can one know that what the DJ says is true? The music that was made then may have been of similar quality as most of the music that is produced now, with a few exceptions that are remembered as “classics.” But since the DJ (thankfully) did not play all the bad songs from the record and only remembered the requested classic, the DJ’s assessment of the past, where music seemed so much better, could have been biased.

In epidemiology, this bias of the DJ’s assessment is known as “survivor bias,” which is a common feature in epidemiological studies. Survivor bias can be defined as selective availability of information only on “survivors.” In observational studies, survivor bias can occur when participants are selected while already being exposed for some time to medication, chronic disease, or diet. They are called “prevalent users” and can distort associations between several exposures and disease outcomes. For instance, suppose you seek advice from a very old person about how he or she became old. What if the old person tells you that he or she couldn’t have made it without smoking a pack of cigarettes daily?—This is a typical example of survivor bias as most people who made the poor health choice of smoking a pack of cigarettes per day cannot tell you about that choice anymore, only the ones who survive up to old age and who are the rare exception can. For the smoking advice, the distortion is obvious, but what if the old person told you that he or she couldn’t have made it thus far in life without eating fish daily, or because of taking food supplements like fish oil or multivitamins?

In epidemiologic studies on nutrition, the only way to definitely overcome the issue of survivor bias is to ask, register, or measure nutritional status at the time that someone decides to first eat fish, take food supplements, etc., and then follow the person until the event of outcome, often death or disease, while taking the persistence to the nutritional variable of interest into account. Next, the epidemiologist should contrast these findings to those who did not expose themselves to the nutritional variable of interest and then adjust for potential confounding factors. This is a hard and often impossible task, as study participants are regularly not asked or simply do not know when they started the nutritional exposure of interest. Worse, they may already have died or developed the disease outcome of interest years ago, for which reason they could not be included in the observational study.

Survivor bias is often hidden in the results and sometimes so well hidden that it is not observed. For instance, an observational cohort study examined the level of wine consumption and total mortality among elderly adults.¹ Authors found that wine drinkers had a lower risk to die than teetotalers.¹ However, there was a dose response effect noted in the study, i.e., elderly high wine-consumption drinkers had a lower mortality risk than low wine-consumption drinkers.¹ As this result comes from a study performed in prevalent users, it might be explained by survivor bias. That is, some of the high-consumption wine drinkers may already have died because of heavy alcohol drinking before they entered the study. Only the high wine-consumption drinkers who were fit enough to enter the cohort could therefore participate. Next, they were compared with low wine-consumers and teetotalers, a group in which individuals at high risk of death were not yet depleted at time of inclusion, resulting in the observed

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dose response effect. Other studies have shown that the beneficial effect of moderate alcohol drinking on the risk of death might, at least in part, be explained by the inclusion of prevalent users leading to survivor bias.² Here the problem lies in the definition of the teetotalers. Studies that excluded former and occasional alcohol consumers from the teetotaler reference group (i.e. prevalent users) show no evidence of protection from moderate alcohol consumption.² The underlying theory is that as people age and become unwell, they are more likely to quit or considerably reduce their alcohol intake, leading to an overestimation of “poor health” in teetotalers. For cardiovascular disease, similar issues might explain the paradoxical finding that in observational studies of prevalent users, vitamin and antioxidant supplements prevent against cardiovascular diseases,³ while a meta-analysis of randomized trials found no beneficial effect of these supplements on cardiovascular disease.⁴

A devastating example from survivor bias comes from studies on the effect of hormone replacement therapy (HRT) on coronary heart disease. HRT is prescribed to postmenopausal women to reduce menopausal complaints and it was long thought that it also reduced coronary heart disease, as an additional benefit. The Nurses' Health Study seemed to confirm this when they published results from their observational cohort in 1985 and showed that HRT use was associated with a reduced risk of coronary heart disease in postmenopausal women.⁵ Although this result was immediately contested,⁶ the study report had a large impact on HRT treatment in postmenopausal women. In the United States only, the yearly number of HRT prescriptions increased from 13.6 to 31.7 million between the 1980s to early 1990s.^{7,8} However, when results from a randomized trial came in, 18 years later, it turned out that postmenopausal women who used HRT had an *increase* in risk of coronary heart disease.⁹ The discrepancy between the trials and observational studies could be explained by HRT intake related to time.¹⁰ In the trial, HRT did increase the risk of coronary heart disease during the first years of use, after which it waned.⁹ The analysis of the observational studies, however, mostly contrasted users who had been taking HRT for some time at enrollment (prevalent users) to never users. Most prevalent users were past the initial window wherein coronary heart disease risk was increased and were in a phase of decreased incidence (this phenomenon, characterized by an initial peak in risk, followed by a decrease in risk thereafter, is also known as “depletion of susceptibles”).¹⁰ When observational data were reanalyzed according to time since start of therapy (i.e. by including incident users only), the same pattern emerged as that from the trials, i.e. an increase in risk.¹¹ The lesson learned from the HRT controversy is that in observational studies one should not forget those who did not survive or developed the disease outcome of interest before the study started including participants.

In this issue of *RPTH*, Isaksen and colleagues provide data on dietary intake of marine n-3 PUFAs (a combination of intake of fish and use of fish oil supplements) of 21,970 individuals in the Tromsø study.¹² Information on dietary intake of marine n-3 PUFAs was taken at baseline, after which participants were followed. Authors found that individuals who took the highest amount of marine n-3 PUFAs had a 22%-26% lower risk of first

venous thrombosis. The authors rightly conclude that this finding suggests a protective effect of fish and fish oil supplements to the risk of venous thrombosis. Even though survivor bias might seem unlikely as it seems not likely that intake of marine n-3 PUFAs leads to a sudden increase in risk of venous thrombosis, which later wanes of, as was found in the HRT studies on cardiovascular disease,¹¹ some caution is warranted. First, individuals who were taking marine n-3 PUFAs in the highest amounts were on average 15 years older than those who took the lowest amount of marine n-3 PUFAs and the reason for this large age difference was not explained. Second, even though survivor bias may seem unlikely to explain the authors' findings, there are examples that show that one must be cautious when observational studies show promising results to disease outcomes with ‘harmless’ exposure. For instance, randomized studies on vitamin B supplements, which were thought to reduce the occurrence of venous thrombosis and cardiovascular disease,¹³ found no protective effect on venous thrombosis,¹⁴ but a potential increase in risk of cardiovascular disease.¹⁵ Similarly, observational studies on calcium intake, that included prevalent users, found protective effects on the risk of cardiovascular disease,¹⁶ while the reverse was found when individuals were randomized to calcium supplements,¹⁷ suggesting again that survivor bias might have played a role in the initial protective findings. Although marine n-3 PUFAs may not be harmful, recent clinical trial evidence from the Vitamin D and Omega-3 Trial (VITAL) showed that dietary supplementation with marine n-3 PUFAs does not result in a lower incidence of major cardiovascular events than that with placebo.¹⁸ However, VITAL did not provide outcome estimates on venous thrombosis. For these reasons we would not advocate to advise individuals to take marine n-3 PUFAs to reduce their risk of venous thrombosis based on the findings from Isaksen et al alone.¹² Nevertheless, the finding is intriguing, and at least deserves replication in observational studies or possibly in some small trials that could look into the effect of marine n-3 PUFAs on the coagulation system.

In the end, the association between marine n-3 PUFA intake with a reduced risk of venous thrombosis may be true, just as the feeling of the DJ that “they do not make songs like they used to” may be true, because the possibility of survivor bias alone, similar to a feeling of nostalgia alone, does not rule out that good songs were produced more often in the past than they are now and that marine n-3 PUFA does decrease the risk of venous thrombosis.

RELATIONSHIP DISCLOSURE

The authors state that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

WML and SCC were the main investigators of the manuscript. WML wrote the first draft of the manuscript and the final version. SCC was responsible for review of the manuscript.

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