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CARDIOVASCULAR AND SURVIVAL PARADOXES IN DIALYSIS PATIENTS: What Is So Bad about Reverse Epidemiology Anyway?

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What Is So Bad about Reverse Epidemiology Anyway?

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ABSTRACT

The term "reverse epidemiology" is used to indicate that such surrogates of cardiovascular risk and metabolic syndrome as obesity, hypercholesterolemia and hypertension are paradoxically associated with greater survival in individuals with chronic disease states and wasting, including dialysis patients, in whom the short-term survival is the issue at hand. It is being debated whether the crossing curves of the obesity-mortality association in dialysis patients vs. the general population reflect the residual confounding that needs to be controlled away statistically, or whether they have biological plausibility in sharp contradistinction to the currently dominating Framingham paradigm. In the rush to define the crossing curves as statistical artifact and to dismiss the term "reverse epidemiology" as a misnomer, we may miss the opportunity to gain information housed in those crossing lines and may miss the bigger picture, i.e., how to improve longevity in dialysis patients. Even though some of the survival paradoxes in dialysis patients appear to fulfill the Hill's criteria of causation, there are still two major drawbacks: (1) convincing pathophysiologic pathways to link dialysis patient survival to obesity, fat accumulation, higher serum lipoprotein levels or slightly higher than normal blood pressure values are yet to be verified in animal and other scientifically sound models; and (2) randomized controlled trials need to show that nutritional interventions resulting in weight gain can lead to greater survival in dialysis patients. Studying the survival paradoxes may lead to a paradigm shift by establishing targets beyond the Framingham guidelines for populations with chronic disease states.

"The purpose of science is not to analyze or describe but to make useful models of the world. A model is useful if it allows us to get use out of it."

—Edward De Bono

The Framingham Paradigm

The Framingham studies, which are all observational-epidemiological in nature, have played a crucial role in formulating what is considered the contemporary or conventional principles of cardiovascular risks (1). The Framingham Heart Study began in 1948 with 5209 adult subjects from Framingham, MA, and is now on its third generation of participants (2). The premises of the Framingham paradigm are based on the notion that certain exposures or conditions, called cardiovascular risk factors, are invariably associated with higher risk of atherosclerotic cardiovascular disease and poor survival. Tobacco smoking, diabetes mellitus, hypertension and hypercholesterolemia are considered the major modifiable risk factors in the general population (3). Other risk factors such as surrogates of metabolic syndrome including obesity and hypertriglyceridemia and inadequate exercise are also considered as additional components of the Framingham paradigm, albeit with less consistency than the major risk factors. Both basic science studies and clinical interventional trials have served to support the observational findings of the Framingham principles such as the "causal" role of the LDL-hypercholesterolemia in cardiovascular disease and death (4). However, it is important to note that Framingham Heart Studies were and still are observational and hence amenable to the same inherent limitations of other observational studies.

Causal Inferences in Observational Studies

In epidemiological studies, the natural occurrences of the events of interest are "observed" in a given population. Neither an external "intervention" is introduced to induce an event, nor is a "randomization" implemented for an intervention. The ultimate goal of the epidemiological studies is to disclose the unbiased association between the candidate exposures – also called "risk factor" – and the "outcomes" of interest in the study

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population and then to extrapolate it to a larger population. This association, however, is often distorted by the third factors called "confounders". Due to the lack of randomization, which would have effectively nullified the effect of confounders, the epidemiological associations are invariably subject to confounding bias. No matter how rigorous the confounders are adjusted for in multivariate models, there are invariably unknown confounders that may be the reason for the observed associations. As a result, the inability of the observational-epidemiological studies in proving causality is generally accepted as an inherent limitation of the epidemiology no matter what kind of sophisticated multivariate techniques are employed (5).

Despite the foregoing nihilistic view to the causal inference in epidemiological studies, epidemiologists strive to find methods to approach causality. A set of criteria for making the leap from association to causation was systematically presented in the 1965 article of Sir Austin Bradford Hill, "The Environment and Disease: Association or Causation" (6), in that nine criteria to "suggest" causality are named (Table 1). As an example, "temporal relationship" indicates that the exposure, say hypertension, should precede the outcome, say cardiovascular death. There are novel epidemiologic techniques such as structural nested modeling that can better account for time-varying confounders and that are sometimes called "causal models" (7–9). Hence, even though the epidemiology is primarily about the associative and not causal inferences, it can advance steps in the direction of causality.

Causality in Framingham and Newer Paradigms

The fact that is commonly ignored is that many landmark studies, including the Framingham Heart Study, which have implied hypercholesterolemia or hypertension as the possible "causes" of the cardiovascular disease epidemic of the late 20th and early 21st century are observational (1). Even though subsequent randomized

TABLE 1. Hill's criteria for causal inference in epidemiological studies (6). The causality criteria are examined for the so-called "Obesity Paradox" of dialysis patients as a concrete example

	Criterion	Definition/comments	Example of Obesity Paradox in dialysis patients
1.	Temporal relationship	Exposure always precedes the outcome.	Gaining body weight or fat is associated with "subsequent" improved survival in dialysis patients (17,22).
2.	Strength of association	The stronger the association, the more likely it is that the relation is causal.	The death hazard ratio of losing weight is greater than that of other known cardiovascular death predictors such as hypercholesterolemia or hypertension (43).
3.	Dose response	Increasing amount of exposure increases the risk proportionally.	The larger the amount of weight loss, the greater the subsequent mortality (17).
4.	Consistency of results	The association is consistent when results are replicated in studies in different settings using different methods.	Different cohorts [USRDS (111), DOPPS (109), Fresenius (112), DaVita (17), etc.] have indicated similar associations between obesity and greater survival in dialysis patients.
5.	Biologic plausibility	The association agrees with currently accepted understanding of pathological processes. However, studies that disagree with established understanding of biological processes may force a reevaluation of accepted beliefs.	The biological plausibility of obesity paradox appears counterintuitive; however, several recent studies have advanced biologically plausible hypotheses, such as visceral compartment hypotheses (55), endotoxin-lipoprotein hypothesis (49), etc. (see Table 2)
6.	Experimentation	The condition can be altered (prevented or ameliorated) by an appropriate experimental regimen.	Preliminary data have shown that nutritional interventions associated with weight gain appears associated with better nutritional status (74). However, randomized controlled trials are still nonexistent.
7.	Specificity	If possible, a single putative cause produces a specific effect.	Higher adiponectin from fat tissue can be the main cause of survival advantages of obesity (113). However, other causes may also contribute to the obesity paradox!
8.	Biologic coherence	The association is consistent with the natural history of the disease.	… but the obesity paradox appears in contradistinction to the contemporary hypotheses that relate obesity to poor survival!
9.	Analogy	There are similar associations in other populations or under different settings.	Obesity paradox has been observed in heart failure, (26) rheumatoid arthritis (27), cancer (28,29), AIDS (30,31), chronic pulmonary disease (32), coronary artery disease, (33) and in the geriatric populations (37–42).

trials have shown that reducing blood pressure or serum LDL-cholesterol leads to greater survival, these interventions do not necessarily imply causation. Hence, even these so-called conventional cardiovascular risk principles have causality flaws and, therefore, subject to revision and paradigm shift.

As an example, it is possible that the cholesterol reducing agents statins have other salutary effects, such as anti-inflammatory features, that are the main reasons for the improved cardiovascular outcomes in those who take statins. Indeed it was recently shown that statins can more strongly improve cardiovascular events and death if serum C-reactive protein is decreased (10,11). Hence, one may advance the hypothesis that lowering LDL-cholesterol may be an epiphenomenon with little impact on cardiovascular survival. These hypotheses would have sounded highly counterintuitive and unacceptable 10 to 15 years ago; however, it is now being considered as a potentially plausible hypothesis (12). If additional studies suggest that inflammation has greater impact on atherosclerotic cardiovascular disease that LDL-hypercholesterolemia, a major paradigm shift away from the traditional Framingham way of thinking is imminent.

The Concept of Reverse Epidemiology

There is an unusually high rate of cardiovascular disease and death in the half a million dialysis patients in the USA and several millions throughout the world. This vast cardiovascular disease epidemic was originally attributed to the high prevalence of the conventional risk factors such as hypertension or hypercholesterolemia in dialysis patients (13). However, most epidemiologic studies in dialysis patients have failed to substantiate the role of the conventional risk factors in dialysis population as in the general population. Indeed a randomized clinical trial known as the 4D Study failed to show improved survival by reducing LDL-cholesterol using atorvastatin in diabetic dialysis patients (14).

In the past few years an increasing number of epidemiologic studies in large national databases of dialysis patients have indicated paradoxically inverse associations between classical cardiovascular risk factors and mortality (15,16). Indeed, a worse survival among dialysis patients has been observed with a "low", rather than a high, body mass index (BMI) (17) blood pressure (18), and serum concentrations of cholesterol (19), homocysteine (20) and creatinine (21). Even more ironic are findings indicating that "high" values of these risk factors are paradoxically protective and associated with greater survival. Most recently there have even been emerging longitudinal studies showing that gaining body weight and total fat are associated with improved survival over time (17,22). These apparently counterintuitive observations have been collectively referred to as "reverse epidemiology" (15), "risk factor paradox" (23) such as "obesity paradox" (24), and "altered risk factor pattern" (16). Similar paradoxical associations have been reported in other populations with chronic disease states such as heart failure (25,26), rheumatoid arthritis (27),

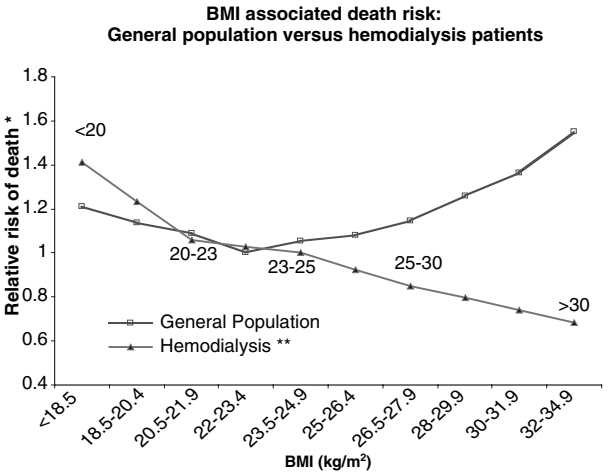

FIG. 1. Crossing curves of the Obesity Paradox: Dialysis patients vs. the general population. Comparison between the impacts of body mass index (BMI) on all cause mortality in the general population (■) versus in maintenance hemodialysis population (▲). The general population data are adopted from Calle et al., NEJM 1999, 341:1097–1105 (combined men and women, healthy, nonsmoker) (108). The hemodialysis data are adopted from Leavey et al., Neph Dialysis Transplant 2001, 16:2386–94 (combined US and Europe data) (109). *Note that each population has a different follow-up period: 14 years for the general population vs. 4 years for hemodialysis patients. **BMI stratifications are different in two populations: X-axis is based on the original graph of the general population, and the original hemodialysis BMI subgroup ranges are printed additionally along the hemodialysis curve. [adapted, with permission, from Kalantar-Zadeh et al. (15)].

cancer (28,29), AIDS (30,31), chronic pulmonary disease (32), coronary artery disease (33), and even earlier stages of chronic kidney disease (34–36) and in the geriatric populations (37–42). Among the above-mentioned cardiovascular risk factors with an inverse association with mortality, the obesity paradox (Fig. 1) has been the most consistent one and is more extensively studied (43,44).

The Biological Plausibility of Reverse Epidemiology

Table 1 shows the evidence for the causal inference of the obesity paradox using Hill's criteria of causation. Even though the biological plausibility and scientific coherence do not appear adequately strong at this point in time, there are a number of recently developed hypotheses that offer platforms for future studies (Table 2). Obesity and/or weight gain may be associated with a more stable hemodynamic status and improved hemodynamic tolerance to afterload-reducing agents (45). Because lean individuals have significantly greater increases in plasma epinephrine and renin levels during stress (46), diminished stress responses of these neurohormonal systems in obese patients may be salutary.

Altered cytokine and neuroendocrine profiles of obese patients may play a role in conferring survival advantages to them (45). Favorable alterations in the tumor necrosis factor alpha system have been observed in obese

TABLE 2. Possible pathophysiologic mechanisms leading to survival advantages of obesity in dialysis patients

Pathophysiologic mechanisms of Obesity Paradox
Time differential of competitive risk factors: overnutrition vs. undernutrition (71)
Dominant role of wasting in chronic disease states (77)
Irrelevancy of risk factors of long-term mortality (68)
Selected genotype resulting from survival selection over the CKD progression (107)
Role of the visceral compartment as the source of uremic toxin (55)
Containment/storage of uremic toxins in fat tissue (24)
Salutary anti-inflammatory cytokines related to fat, including adiponectins (113)
Tumor necrosis factor alpha receptors (47)
Endotoxin-lipoprotein hypothesis (49)
Stability of hemodynamic status in obese patients (45)
Neurohormonal alterations in obesity (46)
Alteration of conventional risk factors in uremic milieu
Protecting role of fat storage during hardship episodes in the history of mankind (69)

patients (47). Obese patients generally have higher levels of lipids including lipoproteins that can actively bind to and remove circulating endotoxins, nullifying the deleterious potential of endotoxins in causing inflammation and subsequent atherosclerosis (48). According to this so-called endotoxin-lipoprotein hypothesis, which also explains the hypercholesterolemia paradox, there is an optimum lipoprotein concentration below which lipid reduction would be detrimental (49,50).

When overweight or obese individuals with higher body fat develop a deficiency in energy or protein intake, they are more resistant to developing frank protein-energy malnutrition. Arguably for this reason, underweight or normal-weight individuals who develop chronic disease states are more likely to fall ill or tend to recover more slowly from illness than those who are overweight (42). To that end, many studies report a strong association between hypoalbuminemia and cardiovascular disease and death in dialysis patients (51–54). Moreover, uremic toxin production rate may be relatively higher in patients with lower BMI due to their relatively larger visceral compartment (55).

Time-Differential of Competing Risks: Short-Term vs. Long Term Survival

In the United States and most industrialized nations, where the life expectancy is the greatest, milestones of "over"-nutrition such as obesity and hyperlipidemia are major risk factors for long-term cardiovascular mortality (56–62). In such nations, individuals can live "long enough" to die of the consequences of conventional risk factors. Studies of risk factors of cardiovascular mortality, such as Framingham Heart Study, are essentially based on these long-living populations, also called "the general population". In contrast, in developing countries, which represent the majority of the world's population, "under"-nutrition is still a powerful determinant of poor clinical outcome and morbidity and mortality, leading to a shorter life expectancy (63–65).

Using the above analogy, survival advantages that exist in obese dialysis patients may, in the "short-term", outweigh the harmful effects of these risk factors on cardiovascular disease in the "long-term". As over two-thirds of dialysis patients are already dead within 5 years of commencing dialysis treatment (66,67), the long-term effects of conventional risk factors on future mortality is essentially irrelevant. In other words, dialysis patients die much faster of short-term effects of such risks factors as "under"-nutrition and inflammation, before they have time to die of Framingham risk factors. Chertow et al. showed that even cancer surveillance in dialysis patients is inconsequential, since they die faster of "other" causes (68). Hence, ironically stated, dialysis patients do not live long enough to die of the consequences of the Framingham paradigm.

What Is Reverse and What Is Normal?

What we consider "reverse" epidemiology, i.e., the stronger impact of undernutrition and short-term death, may indeed be the "natural" epidemiology of mankind, whereas that the so-called conventional epidemiology, i.e. the Framingham paradigm, is a new, unusual and counterintuitive phenomenon in the history of mankind, which has only emerged in late 20th century. In recent decades, excess weight and obesity have become mass phenomena with a pronounced upward trend in most industrialized nations. However, despite the detrimental effects of being overweight, longevity in these nations is longer than ever (69). With advancing age or increasing prevalence of chronic disease states, the detrimental effects of obesity, overnutrition, and hypertension may diminish if not disappear.

Is Reverse Epidemiology an Emerging Paradigm?

Should dialysis patients be encouraged to gain weight if they want to live longer? (24). Or should obese dialysis patients lose weight if they want to be waitlisted for kidney transplantation? (70). What is the optimal BMI for a dialysis or heart failure patient? (71). Should the recommended BMI, lipid and blood pressure targets of the general population be also recommended to dialysis patients? (72). Can nutritional interventions to gain weight (17,73) or to improve appetite (74,75) lead to improved survival in dialysis patients, whose 20% annual mortality is currently worse than most cancers? Can randomized controlled trials be designed using nutritional interventions with anti-inflammatory and antioxidative properties (76) or with orexigenic (appetite improving) agents (74) to examine whether survival improves in dialysis or heart failure populations? Is the reverse epidemiology the hallmark of all populations with chronic disease states

or wasting syndrome? (77). What defines a "population" with reverse epidemiology?

The purpose of this commentary is not to provide answers to these somewhat philosophical questions but to reopen them for debate. The focus of the debate between the proponents and opponents of the reverse epidemiology should be over its "biological plausibility". Being obsessed with proving or disproving a mere terminology (78) does not help the patients, nor does it advance the field. If gaining weight (17) including body fat increase (22) confers greater survival in dialysis patients, and if such an effect can be shown in randomized controlled trials, then this should be recommended to dialysis patients, no matter how many old paradigms and principles are refuted. Similarly, if controlled trials show that weight loss, reducing LDL cholesterol or treating even mild to moderate hypertension is associated with greater survival in dialysis of heart failure patients, then the reverse epidemiology will become yet another refuted hypothesis in the history of medicine and science. The future will show whether we are heading to the "beyond Framingham" territory or not (79).

Why So Much Resentment against Reverse Epidemiology?

The counterintuitive epidemiologic findings in dialysis patients and other similar populations with chronic disease states have contributed to the growing confusion and have left nephrologists and other physicians with the ongoing dilemma as to whether or not to treat obesity, hypercholesterolemia, hypertension, or hyperhomocysteinemia in dialysis patients (16). This confusion was further aggravated when the 5-year randomized, double-blind, placebo controlled 4D trial in over 1200 diabetic dialysis patients failed to show any significant survival advantage of reducing LDL-cholesterol by atorvastatin (14), which has been effective in other interventional trials in the general population (80). Despite the striking consistency of the data in both observational and interventional studies, there has been a major disbelief, mostly by the nephrology community, that these findings are false and misleading.

Some senior nephrologists find it hard to believe that decades of emphasis and spending time on treating hypertension and hypercholesterolemia in dialysis patients have been inconsequential. Some academicians who have spent a life-long career in examining the links between conventional cardiovascular risk factors and cardiovascular disease in renal failure may feel threatened by this and other newer concepts that question the very foundations of the Framingham paradigm. Many critics of the reverse epidemiology underscore the lack of biological plausibility for these "counterintuitive" associations and call it "residual confounding" that needs to be adjusted for. Some critics, however, have focused their efforts on criticizing the term "reverse epidemiology" by calling it a misleading misnomer and try to indirectly discredit the concept by attacking its terminology (78).

Is "Reverse Epidemiology" a Misleading Misnomer?

To our knowledge, the term "reverse epidemiology" was first mentioned by some epidemiologists in the Center for Disease Control and Prevention and the National Cancer Institute (NCI) in late 1990's in conjunction with the novel near real-time DNA fingerprinting to identify clinical isolates of food-borne pathogenic bacteria or cancer cells (81,82). This new methodology, by enabling early recognition of food-borne disease clusters as the source of outbreaks, appears to circumvent the traditional outbreak investigations that are usually initiated by epidemiologic methods as the first step to be followed by focused biochemical investigations. The "reverse epidemiology" indicates the reversal of epidemiology-biochemistry hierarchy in contrast to the traditional outbreak investigations (81). Similarly, the NCI cancer epidemiologists used the term "reverse epidemiology" in the context of the ability to look at genetic changes in cancer cells to the search for external causes of cancer, again circumventing the traditional need to conduct a priori epidemiologic analyses (82).

It appears that the term "reverse epidemiology" was first introduced to the nephrology arena by Coresh during his lecture at the 1999 American Society of Nephrology annual conference in Miami, FL (78). Subsequently, Kalantar-Zadeh et al. repeated this terminology in several publications including a Perspective in Renal Medicine article in "Kidney International" in March 2003 (15), in that the concept of reverse epidemiology was systematically described in dialysis patients. Kalantar-Zadeh et al. also introduced this concept in a cardiology journal to describe the similar counterintuitive associations in heart failure patients (26). Since then the notion of reverse epidemiology has found to be even more inclusive, as it has gone beyond the dialysis and heat failure patients (71) and now relate to a number of different populations with chronic disease states and wasting syndrome including geriatric populations (77). It is estimated that almost 30 million Americans with chronic disease states or advanced age exhibit a reverse epidemiology (77). Hence, in approximately 10% of the US population, the Framingham paradigm based recommended target ranges for BMI, lipid or blood pressure may not apply and may even cause more harm than help.

Any new scientific concept should have an appropriate terminology to be optimally represented. The term "reverse epidemiology" has been criticized with the argument that the science of epidemiology cannot be reversed (78,83). This reasoning is indeed surprising, because it must be clear to such astute critics that the term does not pertain to the entire field of epidemiology. This is not the first time that the word "reverse" is used in association with the name of an entire discipline to indicate a focused concept. There are indeed such similar terminologies as reverse genetics (84), reverse pharmacology (85), reverse physiology (86), reverse cardiology (87), reverse endocrinology (88), reverse immunology (89), etc. Each of these designations has very specific focus and does not imply that the field of genetics,

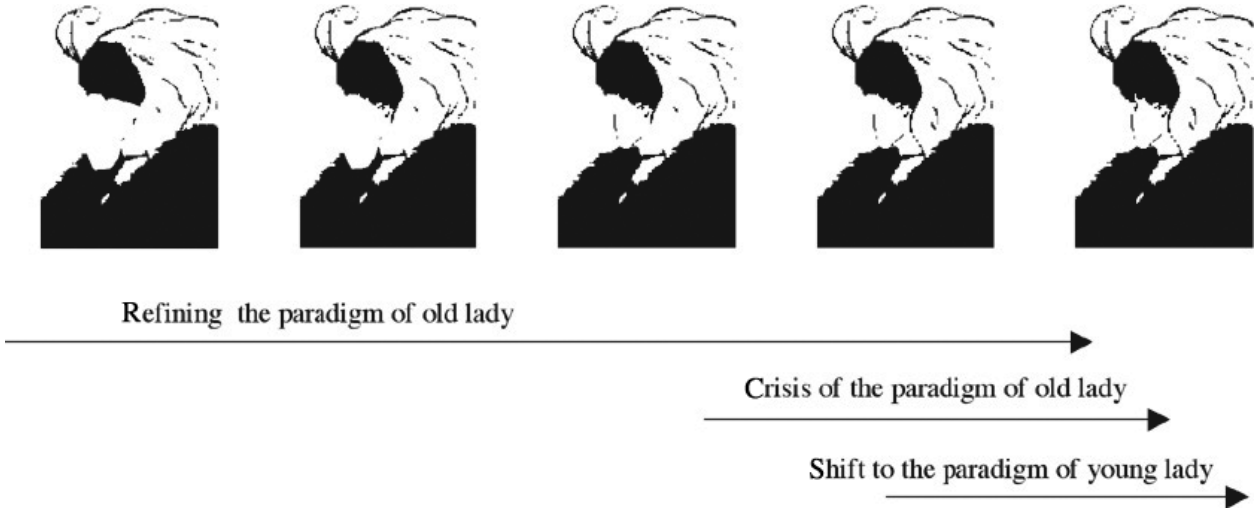

FIG. 2. The model of the paradigm shift by A. Kurakin, based on the original Old/Young Lady Gestalt [adapted with permission from Alexei Kurakin (110)].

pharmacology, physiology, cardiology, endocrinology or immunology is reversed. The critics are encouraged to focus on the flaws of the concept of reverse epidemiology rather than being obsessed with the terminology.

In the past 5 years, the term "reverse epidemiology" has been established as a recognized scientific term and used by many authors (16,83,90–97). The term has been incorporated by the "National Library of Medicine" as a valid search term. At the time this paper is edited (June 2007) PubMed has listed over 40 articles that include the term "reverse epidemiology" in their titles or abstracts. In Google search, there are over 300 websites on reverse epidemiology and over 13,000 websites that are cross-referred to reverse epidemiology. In February 2006, the concept of reverse epidemiology was found to be the leading "emerging research front" in the entire field of clinical medicine (98). This exponential growth and recognition can only indicate that there must be some degree of scientific appeal with both the term and the concept of reverse epidemiology.

What Is So Bad About Crossing Curve Anyway?

The "crossing curves" of the obesity-mortality (Fig. 1) or cholesterol-mortality relationships in dialysis patients vs. the general population (15) have been a matter of concern for some, who suggest that reverse epidemiology is nothing but a "residual confounding" (83,94,95). Some critics call the reverse epidemiology a mere observational paradox or statistical artifact "lacking biological plausibility" to be understood only to the extent that it can be explained away by using good analytical tools (83). On these lines, Liu et al. (99) showed that reverse epidemiology of hypercholesterolemia is observed only in those dialysis patients who have malnutrition-inflammation syndrome, especially as a simple stratification could produce unbiased results and explain away the crossing curves. However, it was never clarified what to do with over 2/3 of the dialysis patients of the same cohort who were malnourished or inflamed and who had a crossing curve (100). Should this majority group of patients be ignored as they are irrelevant statistical artifact? Interestingly, the large randomized controlled trial that was published after Liu's observational study (99) [the 4D Study (14)] showed that lowering cholesterol even in diabetic dialysis patients did not improve survival. Yet, these consistent findings are dismissed by some critics of reverse epidemiology as results of "the bad luck" (78). If the crossing curves are merely simple artifacts due to residual confounding, it is not clear how uncrossing the curves is relevant when even the controlled trials fail to prove the point.

Perhaps we should not be so quick to model away the crossing curves illustrated in Fig. 1. In the rush to define the crossing curves as paradoxical, we miss the opportunity to gain information housed in those crossing lines. The causes of reverse epidemiology are by and large unknown. Although the mainstream thinking originating from the Framingham paradigm tends to explain away the paradox as statistical confounding, other investigators continue to report more populations with reverse epidemiology (101–106).

Conclusions

The unacceptably high mortality of dialysis patients has not substantially improved despite widespread use of antihypertensive and lipid-lowering medications. In sharp contradistinction to the Framingham principles, obese, hypercholesterolemic and hypertensive dialysis patients live longer than those having values within the general population's "normal" range. Given our ignorance of the causes of this reverse epidemiology and of whether its underlying cause influences survival, it is plausible that obese or hypercholesterolemic dialysis or heart failure patients actually have "real" survival advantages compared to the nonobese or

normocholesterolemic patients. The reasons for these survival paradoxes are not (currently) apparent, but several speculations come to mind (Table 2).

Some of the survival paradoxes in dialysis patients, such as the obesity paradox, fulfill most of the Hill's criteria of causation. However, there are still two important "missing" components: (1) Animal models or other scientific evidence for convincing pathophysiologic pathways to link dialysis patient survival to obesity, fat accumulation, higher serum lipoprotein levels or slightly higher than normal blood pressure values; and (2) Randomized controlled trials to examine whether nutritional interventions resulting in weight gain can lead to greater survival in dialysis patients. Studying the survival paradoxes may lead to a paradigm shift by establishing targets beyond the Framingham paradigm guidelines for populations with chronic disease states including dialysis patients.

As physicians and scientists with professional integrity committed to the "cause-no-harm" motto, we should feel uneasy by the readiness with which the Liu et al. (99) dismiss the paradoxical associations as mere confounding without biological plausibility and replace them with the more speculative concept that cholesterol should be lowered in all dialysis patients no matter what. We must not lose sight of the fact that our task as scientists, physicians, epidemiologists, or public health advocates is to try to understand the underlying biology of survival paradoxes with the goal of developing interventions to improve the outcomes of the almost 30 million Americans suffering from chronic disease states. The true value of these approaches is not whether they can "explain away" the crossing of the curves of the reverse epidemiology depicted in Fig. 1. We should not focus too much on whether we can uncross the curves by statistical tools. Rather, the focus should be on what the crossing curves might teach us about genetic and environmental influences on the survival of these patients (107), and on what they might teach us about the triggers for reverse epidemiology and the factors influencing the sensitivity of these triggers. Let's be rightfully obsessed with good science, good medicine and good patient care and channel our concerns and emotions for the greater good instead of being obsessed with terminologies or feel threatened by paradigm shifts. After all, improving the longevity of dialysis patients is a win-win situation for all of us, no matter what terminologies we use.

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Relevant Conflicts of Interest

None declared by the author.

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