Editorial

A big data approach to examine the association of high density lipoprotein cholesterol and mortality: lessons for future investigations

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Introduction

It has been a long-held understanding that higher levels of high density lipoprotein cholesterol (HDL-C)—colloquially referred to as the good cholesterol—are associated with reduced risk of cardiovascular events and death. The seminal observations were made in a 1988 report of 2,748 individuals from the Framingham Heart Study (1) where after 12 years of follow up, the researchers reported that compared to the highest quintile of HDL-C, the lowest quintile had increased risk of death from coronary heart disease in both men and women. The fundamental assumption of the analytic strategies undertaken by the Framingham investigators, which we later learned was not valid, was that the relationship between HDL-C and risk of death is linear where low levels of HDL-C are associated with increased risk, and higher levels are associated with reduced risk of death from coronary heart disease. Decades later, and thanks to the power of big data, our understanding has evolved as we have come to appreciate that the association between HDL-C and risk of death is not linear. The implicit assumption of linearity and comparison of risk in high HDL-C *vis-à-vis* low HDL-C groups (e.g., quintile 5 *vs.* quintile 1 in the Framingham studies), when the risk relationship might not be linear and risk may be increased at both ends of the HDL-C values spectrum, might obscure the presence of an association where one exists (2).

The observations from the first Framingham studies were reproduced in several other relatively small cohort studies (compared to today's big data cohorts) which also analytically linearized the relationship between HDL-C and risk of death; those observations went unchallenged for many decades, and supported the hypothesis that raising HDL-C levels will lead to decreased risk of death. However, clinical trials designed to test this hypothesis were met with failure when studies of cholesterol ester transfer protein (CETP) inhibitors and niacin resulted in significant improvement in HDL-C levels, but did not yield significant reductions in adverse cardiovascular outcomes or mortality (3,4). Recent Mendelian randomization analyses showed that genetic mechanisms that raise plasma HDL-C did not result in reduced risk of myocardial infarction (5). Given this background, recently Bowe *et al.* took a big data approach to characterize the association between HDL-C and risk of death in a cohort of 1.7 million United States veterans followed for over 9 years and described-for the first time-a U-shaped association between HDL-C and risk of death in that both low and high HDL-C levels were associated with increased risk of death (6). In another study of 1.9 million United States veterans followed for 9 years, Bowe *et al.*

reported that both low and high HDL-C were associated with risk of increased risk of incident chronic kidney disease, kidney disease progression, and end stage kidney disease (7). Taken together, these studies suggest that (I) the relationship between HDL-C and risk of death is not linear and; (II) HDL-C is a confounded measure and is a non-specific cardiovascular risk factor associated with non-cardiovascular outcomes (6,7).

The findings were very nicely reproduced in the study of Ko *et al.* who examined the association of HDL-C with cardiovascular and non-cardiovascular mortality in an observational cohort of 631,762 individuals from the Cardiovascular Health in Ambulatory Care Research Team datasets. The investigators reported that individuals with lower HDL-C had higher risk of cardiovascular, cancer, and other mortality. Notably, individuals with higher HDL-C levels had also increased risk of non-cardiovascular mortality. The study also reported significant associations between HDL-C levels and sociodemographic, lifestyle, and comorbidity parameters suggesting that HDL-C is a profoundly confounded marker and given that it is also associated with non-cardiovascular outcomes, it may lack specificity as a potential marker of cardiovascular events (8).

Most recently, Madsen *et al.* examined the hypothesis that extreme high concentrations of HDL-C are associated with increased all-cause mortality in men and women (9). The investigators used data from two prospective population-based studies: the Copenhagen City Heart Study and the Copenhagen General Population Study. The overall cohort was comprised of 52,268 men, and 64,240 women (9). During 745,452 person-years of follow-up, the relationship between HDL-C concentrations and risk of all-cause mortality exhibited a U-shaped association for both men and women (9). The investigators concluded that in both men and women from two general population Northern European cohorts, high concentrations of HDL-C were paradoxically associated with increased mortality risk (9).

Although the epidemiologic evidence is consistent in multiple cohorts and a variety of settings and although the evidence is congruent with results derived from Mendelian randomization studies and might explain the failure of randomized controlled trials aimed at increasing HDL-C levels in improving outcomes, the mechanism underlying those observations remains unclear. One possible explanation is that HDL-C is a non-specific heavily confounded biomarker; and is not an independent modifiable risk factor for cardiovascular disease; therefore, targeting it by pharmaceutical interventions is not likely to yield improvement in cardiovascular outcomes or death. Other explanations are rooted in experimental evidence showing that HDL-C displays a biphasic effect (at low and high concentrations) and that the beneficial effect of HDL-C is reversed at high concentrations where it paradoxically promoted senescence and impaired endothelial progenitor cell tube formation and angiogenesis (10).

Big data offers new insights

Evaluation of the association of HDL-C and risk of death through a big data lens revealed insights that were not feasibly discernable in prior relatively smaller studies. A reasonable analogy to better appreciate the power of big data is to consider the difference between a light microscope and an electron microscope. Examination of a biologic specimen under a light microscope reveals important insights, but further examination with an electron microscope reveals more nuanced and detailed picture. Similarly, examining an epidemiologic association using a big data approach is akin to looking at it through an electron microscope which would reveal a richer, more detailed, and a higher resolution characterization that would be challenging to discern using a smaller cohort.

The evolution of our understanding of the association between HDL-C and risk of death invites us to contemplate on what other assumptions in clinical medicine—we hold true today—that would turn out to be incomplete or invalid when revisited and re-examined through the lens of big data. A big data approach might provide further insight and offer significant value that should be realized through innovative research endeavors to challenge prior assumptions, and fill important and consequential knowledge gaps (11-13). We predict that the pursuit of big data research will very likely upend several long-held assumptions, and as a result will enrich our understanding of health and disease and favorably impact the human condition.

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Footnote

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