Bilirubin, Gallstones, and Mendelian Randomization

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Gallstone disease causes a substantial health and economic burden in the United States and other developed countries. More than 6 million men and 14 million women aged 20 to 74 years in the United States have gallbladder disease.\(^1\) Approximately 650,000 to 700,000 cholecystectomies are performed annually in the United States, and the costs associated with the symptoms and complications of gallstones are estimated to be $6.5 billion per year.\(^2\) Known risk factors for gallbladder disease include obesity, recent weight loss, age, hormone use, parity, lack of exercise, and alcohol use.

We found the article by Stender et al interesting clinically and methodologically. First, using observational data and multivariable analysis to adjust for a variety of known risk factors for gallbladder disease, the authors demonstrate that an elevated plasma bilirubin level is associated with a greater likelihood of symptomatic gallbladder disease. Second, using a technique referred to as mendelian randomization, the authors took advantage of the random assortment of genes that occurs during gamete formation. They demonstrate that a genetic variant that is associated with increased plasma bilirubin levels is associated with an increased likelihood of symptomatic gallstone disease. Because the exposure (the genetic variant) is random, the genetic analysis increases the likelihood that the relationship between plasma bilirubin and symptomatic gallstone disease is causal.

As the human genome is increasingly defined, it is likely that mendelian randomization can become a valuable tool to help confirm or refute whether relationships between other risk factors and diseases are causal.

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