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Bariatric Surgery and Cardiovascular Disease

The Target Trial Emulation Framework Provides Transparency in Articulating the Limits of Observational Studies

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Madenci et al.[1] used the target trial emulation framework to estimate the causal effect of bariatric surgery on the 7-year risk of cardiovascular disease (CVD). They highlighted the pitfalls in the design and analysis of previous observational studies conducted on this topic, which found overall that bariatric surgery lowers the risk of CVD.[2,3] In particular, a central limitation of those studies was the consideration of bariatric surgery as a "point intervention," overlooking the potential role of preoperative components, which could directly affect the risk of CVD. By explicitly specifying and emulating two target trials, Madenci et al. clearly articulated how current recommendations related to bariatric surgery and CVD may be misguided due to being based on potentially flawed observational studies. The use of target trial emulation also enabled the authors to uncover potential limitations of healthcare databases to emulate trials of bariatric surgery.

A FEW WORDS ON THE TARGET TRIAL EMULATION FRAMEWORK

Robins, Hernán and their team have formally introduced the target trial emulation framework[4,5] and highlighted the importance of harmonizing the protocol of the hypothetical (target) trial with that of the corresponding observational study. This process has added transparency to the design of observational studies, improved their quality and reproducibility,[6] and has uncovered important and avoidable flaws in previous analyses. There are many examples of observational studies that led to different conclusions than those of corresponding randomized controlled trial (RCTs) due to differences in study design, rather than violations in the standard identifiability assumptions for causal inference (conditional exchangeability, positivity, and consistency). For example, an important flaw in these observational studies was the comparison of prevalent users versus nonusers, instead of initiators versus noninitiators of a treatment (as considered in the RCTs). Two of the most notorious examples are the studies on the effect of hormone therapy on coronary heart disease[7] and statins on cancer.[8] The studies that used the target trial emulation framework for the aforementioned examples[9,10] produced very similar results with the corresponding RCTs and illustrated the importance of well-designed observational studies for health research.

The target trial emulation framework is a useful tool in the arsenal of epidemiologists and medical researchers. However, the use of this framework does not guarantee that the results are accurate, as the validity of the findings strongly depends on the quality and the features of

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the data. In particular, unlike in RCTs, unmeasured confounding is not addressed by design, and therefore successful target trial emulation relies on information on specific confounders from sufficiently rich healthcare databases. More generally, if an observational database is not appropriate to answer a specific research question, then the results may be biased. This issue has been illustrated when evaluating the effect of preventive services with databases of administrative claims in the United States.[11]

IS IT PLAUSIBLE THAT BARIATRIC SURGERY HAS A PROTECTIVE EFFECT ON CARDIOVASCULAR DISEASE BASED ON RCT EVIDENCE?

There is evidence from RCTs that bariatric surgery, compared to medical and/or lifestyle management, is more effective in bodyweight reduction, diabetes remission, and reduction in blood pressure and glycated hemoglobin in individuals with obesity.[12–14] So, it is plausible to hypothesize that bariatric surgery has a protective effect on CVD, as it improves overall the cardiometabolic profile of the patients. It has also been observed that pharmacological interventions that resulted in body weight[15,16] and blood pressure reduction[17] were also associated with reduced risk of CVD. However, bodyweight and blood pressure changes are implemented in a different way through medication versus bariatric surgery, and hence RCTs comparing the effect of bariatric surgery versus other lifestyle interventions on CVD would give a clearer picture. Unfortunately, there are no RCTs with sufficient sample size and follow-up period to evaluate the effect of bariatric surgery on the risk of CVD.

CAN WE ESTIMATE THE CAUSAL EFFECT OF BARIATRIC SURGERY ON CARDIOVASCULAR DISEASE USING OBSERVATIONAL STUDIES?

Bias in Conventional Observational Studies

Observational studies from routinely collected healthcare data allow us to study long-term outcomes and therefore can shed light on the causal relationship between bariatric surgery and the risk of CVD. Most of the published studies that used conventional observational designs (without explicitly describing the hypothetical target trial) have reported a protective effect of bariatric surgery on CVD. Madenci et al.[1] contested these findings, emphasizing potential flaws within those studies. A critical aspect of their criticism was that bariatric surgery encompasses preoperative, operative, and postoperative components, and hence it is not a point intervention as it was considered by previous conventional observational studies.

Specifically, all the previous observational studies have (implicitly) assumed that there was no direct effect of the preoperative procedure on the risk of CVD. However, during this period, lifestyle changes are expected to lead to a reduction in glycated hemoglobin, body mass index (BMI), systolic blood pressure, and triglycerides, and as such, this assumption seems implausible. Hence, we agree with Madenci et al.[1] that differences in presurgery interventions and risk factors are likely to confound the relationship between bariatric surgery and CVD.

Challenges in Emulating Trials of Bariatric Surgery

Madenci et al.[1] emulated two different target trials:

(1) Target trial #1 in which individuals were randomized at the time of bariatric surgery among those who have successfully completed the preoperative period to (i) bariatric surgery and postoperative monitoring or (ii) no surgery during the follow-up.

(2) Target trial #2 in which individuals were randomized to (i) preoperative screening and management components and, if these are successfully completed, bariatric surgery and postoperative monitoring or (ii) no preoperative components and no surgery during the follow-up.

There are certain data limitations in the two trial emulations of Madenci et al.[1] The authors do mention that trial emulation #1 might suffer from differentially mismeasured confounding: individuals who later undergo bariatric surgery have more regular examinations before the surgery and therefore, comorbidities are measured more frequently compared to individuals in the no surgery group, resulting in much higher prevalence of obstructive sleep apnea, osteoarthritis, hypertension, and dyslipidemia. In trial emulation #2, it was not possible to compare individuals who did and did not experience a preoperative period. Hence, it was not feasible to determine adherence to preoperative procedures in the bariatric surgery group. Therefore, the authors could not account for adherence over time, and so they adjusted only for baseline covariates. The authors investigated internal validity by utilizing two positive control outcomes, BMI and glycated hemoglobin. In both emulated trials, a reduction of BMI and glycated hemoglobin was observed, which is in line with existing RCTs, albeit with somewhat different magnitude.[18] Madenci et al.[1] found no evidence of an effect of bariatric surgery on the risk of CVD based on the two target trials. The authors found similar results to other conventional observational studies[2,3] (even if their results were less pronounced) when they replicated their study design, which considered bariatric surgery a point intervention. In other words, given the limitations of the healthcare databases at hand to emulate trials of bariatric surgery, and the potential bias in conventional observational studies, it remains unclear whether we can estimate the causal effect of bariatric surgery on CVD using observational studies.

Future Research in the Field

The performance of RCTs in this area would provide a clearer picture of the effect of bariatric surgery on CVD. However, in the meantime, clinical decision-making will continue to rely on observational evidence. We agree with Madenci et al.[1] that the preoperative period is important and therefore should be accounted for in future studies. For example, replicating the two suggested target trials using other healthcare databases, particularly those including frequent

and rich information on their individuals with obesity, would provide an interesting avenue for future research. It would also be useful analysis to evaluate the direction of bias based on plausible scenarios for target trial #1, by extending bias formulas for mismeasured confounding[19] when using time-to-event outcomes. Moreover, conventional observational analyses that use matching to account for confounding would make more plausible assumptions if they can additionally incorporate specific variables before time zero (e.g., 1 year before baseline) in the matching process. These variables could include obstructive sleep apnea, osteoarthritis, hypertension, and dyslipidemia as well as changes in blood pressure and body weight.[1]

There are two additional issues that could be further explored. First, the effect of bariatric surgery on CVD might be different in other population groups, especially in younger individuals.[20] The median age of the participants in the veterans' study[1] is over 55 years old, so their cardiovascular disease risk might not be reversible (e.g., they may have established atherosclerosis). However, weight or blood pressure reduction through bariatric surgery might be beneficial for CVD for younger individuals, for example, aged <45 years old, with BMI > 35 kg/m^2. Second, previous observational studies have found different effect estimates for different CVD phenotypes, for example, strong protective effect for myocardial infarction and heart failure and less pronounced for atrial fibrillation.[21] So, it would be interesting to implement the conventional observational analysis and the two proposed emulated target trials in a range of CVD outcomes.

A FINAL NOTE: ARE WE DEFENSELESS AGAINST THE CONSEQUENCES OF OBESITY? FOCUS ON EVALUATING WELL-DEFINED WEIGHT LOSS INTERVENTIONS

The findings from Madenci et al.[1] might raise concerns among clinicians, health researchers, and individuals living with obesity. The detrimental effects of obesity on health and healthcare systems around the world have been extensively documented.[22,23] Hence, the conclusion that a popular weight loss intervention, bariatric surgery, might not reduce the risk of CVD in a very vulnerable population group (individuals with BMI > 35 kg/m^2) can raise the question: are we defenseless against the consequences of obesity?

It is well established that individuals with obesity (BMI ≥ 30 kg/m^2) have a higher risk for developing a range of chronic diseases, compared to normal weight individuals (BMI < 25 kg/m^2 and BMI ≥ 18.5 kg/m^2).[24] However, this does not mean that if individuals with obesity lose weight and become normal weight, their risk is necessarily reduced.[25] Weight loss is not a well-defined intervention (people can lose weight in different ways, e.g., reduced caloric intake, increased physical activity, medication, bariatric surgery), which makes it very challenging to estimate its causal effect on health outcomes.[25–27] Additionally, many observational studies used a flawed design to estimate the effect of weight loss on a health outcome, due to their definition of "baseline and adjustment for "baseline confounders."[27]

For this reason, we believe that epidemiologists and medical researchers who use cohorts and electronic health records should focus on evaluating well-defined interventions in individuals with obesity, including bariatric surgery, pharmacological interventions, diet, and physical activity. As demonstrated by Madenci and colleagues,[1] the target trial emulation framework[4,5,9,10] provides a valuable tool to articulate the potential sources of biases in the observational analysis given the data at hand. In this way, we can understand what works to improve the health of individuals with obesity and provide tangible goals to clinicians and policymakers.

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