Amy Attaway

It is well known that both COPD and smoking are known to cause systemic inflammation which can lead to loss of skeletal muscle mass. Therefore, multiple control groups could be used to improve the design of an observational study analyzing skeletal muscle strength through grip strengths in patients with COPD. These multiple control groups could include COPD subjects who are currently smoking, COPD subjects who are non smoking, current smokers who don't have COPD, and healthy controls. By taking into account the additional variable of smoking status, this study would better account for the additional loss of skeletal muscle strength caused by active smoking and measure these differences amongst the multiple control groups.

Wyatt Bensken

The use of multiple controls is useful in observational studies in understanding the effect of a treatment on a given outcome. An important consideration is that, as Rosenbaum writes, the control groups "must differ in some consequential way." In thinking of an example of the utility of multiple control groups I think to a recent project in seeking to understand how clinically documented health-related social needs (individual level markers of social determinants of health) associate with hospital readmission. The idea is that these newer (released with ICD-10) diagnostic variables allow care teams to better manage patients who have specific HRSN in an effort to reduce readmission and improve overall management. In a simple study we could example how those who are diagnosed with HRSN compare to those without HRSN to see if this diagnostic coding is making a difference. We would want to control for demographic covariates (age, sex, race, ZIP code) as well as clinical covariates such as comorbidities which may play a role in readmission. This simple approach would help us but what could be more informative in highlighting the role and utility of these HRSN would be to take a year when these codes were unavailable (pre-2015) and use that as a second control group. Together, we would be able to disentangle if these diagnostic codes are improving the care for people with HRSN and having an impact on our outcome of interest, which is the readmission rate.

Sofija Conic

Weichuan Dong (lightly edited to fit in this space)

This study explores the effect of spatial access to mammography facilities on late-stage diagnosis of breast cancer among women. Spatial access is measured by the distance from one's residential location to the nearest mammography facility, as well as the availability of private vehicles in households. Both longer distance to facility (DTF) and availability of private vehicles in households could potentially increase the difficulty of spatial access to mammography facilities. The variable of vehicle availability (VA) is not available on the individual level and is instead a census tract level estimate of percentage of households with no vehicle available among households with workers. The study population is all women diagnosed with breast cancer in 2017 in Ohio. The outcome is late-stage versus early-stage diagnosis of breast cancer. The covariates include age at diagnosis, race, ethnicity, marital status, primary payer at diagnosis, rural-urban commuting area code, area deprivation index, education attainment, income, employment, and income.

The descriptions of the treated group and three control groups are as follows.

- Treated: long DTF and low percentage of VA
- Control1: long DTF and high percentage of VA
- Control2: short DTF and low percentage of VA
- Control3: short DTF and high percentage of VA

The control groups would tell whether DTF, VA, neither or both have effect on the stage at diagnosis of breast cancer. While this differs from the multiple control groups in Rosenbaum, I would still like to discuss this example. In addition to the multiple control groups, a control outcome is added to the study. The control outcome is late-stage versus early-stage diagnosis of lung cancer (or potentially other cancers with low sensitivity to early diagnosis via screening), which is presumably not affected by the treatment of spatial access to mammography facilities. This involves adding women diagnosed with lung cancer in the same year in Ohio to the study, divided into the treated and three control groups above.

This is to help check whether there are selection biases associated with distance and availability of vehicles. For example, mammography facilities are mostly located in urban or regional centers, so that rurality and other associated factors (e.g. health behaviors) rather than distance to facility and availability of vehicles could have an impact on late-stage diagnosis. If there is a treatment effect on the breast cancer population, we then test the treatment effect on the lung cancer population with an expectation of no effect. If there is a treatment effect on the lung cancer population, we would argue that the outcome of stage at diagnosis of breast cancer may not be due to the treatment but rather due to selection bias due to other factors.

Joshua Froess

An observational study I would want to be a part of would have to do with opioid use disorder. Multiple control groups could benefit a study on this population. For example, an observational study could be about a new type of rehab strategy to get clean. As a researcher you want to observe how this strategy works against previous strategies. You could compare the individuals in your state going to the new type of rehab and compare them to individuals in another state using a different method.

The controls in this situation are similar to the treated group, but are in a different state. To try and account for the fact that the controls are in a different state, multiple control groups can be used. The multiple control groups can consist of another control group in your state that are using an older rehab strategy, but are addicted to something other than opioids. This would make two control groups that have slight imperfections, but together answer whether or not the new type of rehab would work.

The multiple control groups would be better at understanding how effective the new rehab strategy is because the first control group is looking at patients with opioid use disorder undergoing an older rehab. While, the second control group is looking at patients with a different addiction undergoing an older rehab. It could be seen how effective the opioid use disorder group in the new rehab is against other people with opioid use disorder in an older rehab strategy, and people addicted to other drugs in an older rehab strategy. These control groups will also check to see if there are differences between states when it comes to rehabs. Overall, using multiple control groups will add more levels of depth to the study design then just a single control group.

Jesus Gutierrez

The Kampala, Uganda Tuberculosis (TB) household study enrolls the members of households of recently diagnosed pulmonary TB index cases in order to characterize the mechanisms of infection of this particular bacterium. Upon enrollment, each household member undergoes a substantial physical examination as well as laboratory testing to understand the level of risk that each participant has to TB infection. Since HIV infection has been recognized as one of the most important risk factors, this has been used to organize comparison groups within and among households. The four groups of household members that are established are: HIV+/TB+, HIV+/TB-, HIV-/TB+, and HIV-/TB-.

The HIV+/TB- group, now called 'resisters', is of particular interest because they represent a group of individuals with a high risk level of infection who remain uninfected after at least 2 years of follow-up. This group has been compared to all other household members who became infected (HIV+/TB+ and HIV-/TB+) in order to identify particular characteristics that confer resistance to infection. However, I would argue that in order to define this phenotype more clearly, individual comparison should also be made between 'resisters' and HIV+TB+, 'resister' and HIV-/TB+, and more importantly, 'resisters' and HIV-/TB-.

Joseph Hnath

A future research project that I would like to conduct involves differences in risk adjusted reimbursement for Medicaid managed care. From an economic perspective, the structure of a risk adjustment system should influence the care that is provided, which is an idea that doesn't sit well with most clinicians. Expanding on work by Tim Layton that shows evidence of upcoding in Medicare Advantage plans compared to traditional FFS, I would like to incorporate multiple control groups in an analysis of coding trends in Medicaid. The population would be Medicaid enrollees in both FFS and managed care programs, with the outcome as coding incidence for specific codes of interest or aggregate codes / costs, the treatment as changes in risk adjustment reimbursement policies (typically less generous over time), and controlling for many characteristics across patients to reduce variance between plans and states.

The setup would be a two-pronged comparison: within states and between states. Comparisons within states would be as a response to changes in the risk adjustment reimbursement structure, where we would expect to see changes in the managed care populations but not in the FFS. Comparisons between states would look at the magnitude of change in the risk adjustment reimbursement structure to get after a dose-response relationship between these changes on reimbursement and the outcome of coding intensity. The use of multiple control groups both within states between FFS and managed care, and across different states with varying changes in risk adjustment reimbursement, allows for a clearer understanding of the effect of risk adjustment reimbursement structure on the coding intensity of Medicaid patients.

Jason Huang

Using multiple control groups can be helpful in my course project. I am planning to investigate the causal relationship between having children who live far away and the likelihood of feeling sad or depressed. The eligible population, for the sake of this essay, is older Americans who have any children and they don't live with them. The planned comparison would be, comparing subjects whose children live more than 10 miles from them (treatment group) with subjects whose children live less than 10 miles from them (control group).

If we saw an increased risk of feeling depressed in the treatment group when compared to the control group, we might argue that having children who live far away causes the parent to feel depressed. However, if there is a reason that causes the subject to have children living far from them, and is associated with depression, the observed association can be alternatively, or at least partially, explained by the said reason. Perhaps ever being an alcoholic can be such a reason. It is reasonable to suspect that if a parent has ever been an alcoholic, their children will be more likely to move away from them due to various reasons. And, the connection between alcohol and depression is also obvious.

Therefore, we can construct an additional control group, where the subjects in this group are similar to the treatment group in terms of history of alcohol abuse, and their children live within 10 miles from them. This additional control group will make our hypothesis stronger if we observed a higher risk in the treatment group than the other two groups.

Morgan McGrath

The Canadian Hockey Association allows body checking at age 12-13 and up. In the mid-2000s, teams in the Ontario province began introducing body checking at the 9-10 level. This prompted a number of observational studies investigating the effects of earlier introduction of body checking on overall injury rates in youth hockey. This would be an appropriate situation to implement multiple control groups to better understand the underlying phenomena behind the associations found by these studies.

Rather than just comparing injury rates for Ontario players (age 9-10) before and after the rule change, I would include injury data for these teams across a number of years to look for any potential trends in injury rates over time. This would provide greater context for any changes seen before/after the rule change: are the changes within normal rates of injury fluctuation from year to year, or do they represent a deviation from normal?

In addition, I would look at injury rates for 9-10 year old players in other provinces that did not introduce this rule change during the same time frame in which the rule change was introduced in Ontario. This provides an opportunity to compare the effect of the new rule in the same seasons across different populations of players (those exposed to the rule change and those not exposed). If injury rates rose in both provinces, then it would be likely that some factor other than the rule change was responsible for the rise in injuries in that age group.

Laurie Ann Moennich

A quasi-experimental study has can have multiple control groups, meaning, multiple groups who did not receive the treatment or assignment in question of the study. There may be various reasons why each of the members of these control groups did not receive the treatment. It can be informative to have several control groups, each denied treatment for a different reason – this can help us to understand the true effect of the treatment and uncover bias between the different control groups.

In the past year, the FDA released a warning that a class of antibiotics called fluoroquinolones may be associated with the development of aortic aneurysms and aortic dissections. These fluroquinolones are often prescribed for a variety of illnesses such as pneumonia, UTIs, respiratory infections, and more. A quasi-experimental study could have occurred to explore the relationship between antibiotics and the development of aortic aneurysms. The experimental group would be patients prescribed fluroquinolones, and the control groups would consist of patients who receive other classes of antibiotics. After adjusting for observed covariates (such as differences in the patient groups as to why they were prescribed the differing classes of antibiotics, severity of illness, type of illness, etc.), it would be plausible to observe if there was an increase in risk of the development of aortic aneurysm or aortic dissection in those prescribed fluoroquinolones versus the other groups of patients who were prescribed the other classes of antibiotics.

Amin Saad

Observed treatment effects may occasionally reflect the reasons people end up as treated or untreated. Multiple control groups can strengthen the claim that the observed effects between the control and treatment groups are actually related to the treatment itself. In a hypothetical situation, if I was to study the effects of a prophylactic antibiotic (cefazolin) on reducing the rates of postoperative surgical site infections (SSIs) in adult patients undergoing a cholecystectomy, then a useful method to implement is to use multiple control groups.

The studying population will include a treatment group consisting of a group of patients receiving cefazolin preoperatively, a control group receiving no treatment and a second control group that consists of patients already placed on an antibiotic "treatment" regimen consisting of ceftriaxone and Flagel. The fact that the latter patients are already placed on a treatment regimen may affect their chances of receiving the prophylactic drug. Thus, if the rates of SSIs did not differ between both control groups, then we will have more confidence, that after adjusting for observed variables, if a reduction in SSIs is observed in the treatment group, then it will be attributed to the treatment itself.

However, if the rates are different between the two control groups, then the argument would shift towards inferring a treatment effect using both proposed regimens. It will actually encourage us recommend against the use of cefazolin in patients already receiving antibiotics as part of antibiotic stewardship.