# Mediation and Health Disparities

Ashley I Naimi

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## Contents

## 1 Causal Mediation Analysis

The concepts and methods behind mediation analysis became clearer and more principled with the advent of causal inference. Briefly, modern causal inference relies on counterfactual or potential outcomes to rigorously define what we mean by "the effect of" some exposure on an outcome of interest, and then derives the assumptions that need to hold in order for us to be able to use data to estimate these quantities.

As an example, say we were interested in the effect of quitting smoking on death by 1992 in the NHEFS data. Say additionally that we were interested in the extent to which this effect is mediated by mean arterial pressure. To get a sense of what we're asking, let's draw an initial diagram demonstrating these relationships:

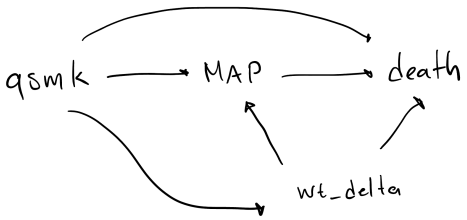


Figure 1: Simple diagram illustrating relationships between quitting smoking, map, death, and weight change in the NHEFS data.

Using causal inference thinking, we could formally define the effect we want to estimate. This effect would have to be based on our fundamental research question of interest. For example, let's say we want to know that the relationship between quitting smoking and death would be if the mean arterial pressure for all individuals in the population was held fixed at some value. We might write this effect out as:

$$E(Y_{1m} - Y_{0m})$$

This equation represents the controlled direct effect of quitting smoking on death if MAP was held at some referent value $m$. This would quantify the risk of death in 1992 that would be observed if everyone quit smoking versus if no one quit smoking, AND if smoking didn't affect mean arterial pressure. To be able to answer this question, we have to get specific about what we will use for the mediator (mean arterial pressure).

For example, let's download the NHEFS data, select our variables, omit

missing data, and begin the process of constructing the variables we need to answer this question.

```
pacman::p_load(tidyverse,
               here,
               lmtest,
               sandwich,
               boot,
               splines)

file_loc <- url("https://is.gd/VPKKsi")
nhefs <- read_csv(file_loc) %>%
  mutate(map = dbp + (sbp - dbp)/3,
         wt_delta = as.numeric(wt82_71 > median(wt82_71, na.rm = T))) %>%
  select(qsmk, map, wt_delta, death, hbp, smokeintensity,
         smokeyrs, hbpmed, age, race, sex, income,
         exercise, cholesterol, diabetes) %>%
  na.omit()

nhefs
```

```
## # A tibble: 1,461 x 15
##     qsmk   map wt_delta death   hbp smokeintensity smokeyrs hbpmed   age  race
##    <dbl> <dbl>    <dbl> <dbl> <dbl>          <dbl>    <dbl>  <dbl> <dbl> <dbl>
##  1     0 122.         0     0     1             30       29      1    42     1
##  2     0  94.3        1     0     0             20       24      0    36     0
##  3     0  88.3        1     0     0             20       26      0    56     1
##  4     0 101.         1     1     1              3       53      0    68     1
##  5     0  90.7        1     0     0             20       19      0    40     0
##  6     0 102.         1     0     0             10       21      0    43     1
##  7     0  90          0     0     0             20       39      0    56     0
##  8     0  68.7        0     0     0              2        9      0    29     0
##  9     0 107          0     1     0             25       37      0    51     0
## 10     0 132          1     1     0             20       25      0    43     0
## # i 1,451 more rows
## # i 5 more variables: sex <dbl>, income <dbl>, exercise <dbl>,
```

```
## #   cholesterol <dbl>, diabetes <dbl>
```

```
plot1 <- ggplot(nhefs) +
  geom_histogram(aes(map,
                     group = factor(qsmk),
                     fill = factor(qsmk)),
                 position = "identity",
                 alpha = 0.5) +
  scale_fill_manual(values=c("#E69F00", "#56B4E9")) +
  scale_x_continuous(expand = c(0,0)) +
  scale_y_continuous(expand = c(0,0)) +
  ylab("Count") + xlab("Mean Arterial Pressure (mm Hg)") +
  theme(text = element_text(size = 10))

ggsave(here("figures", "weight_change_distribution.pdf"), plot = plot1)
```

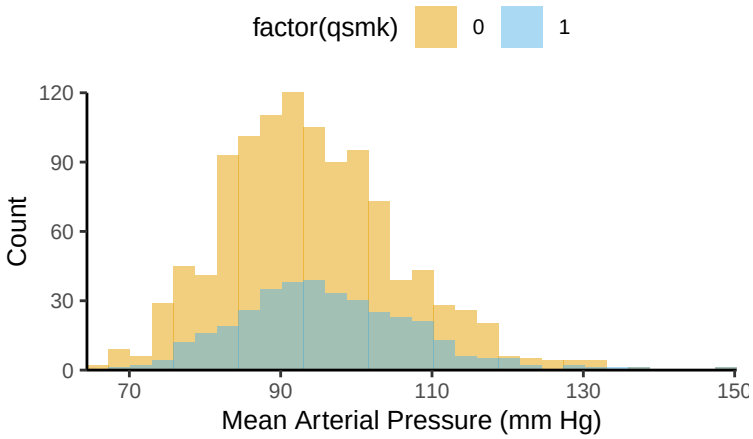


Figure 2: Distrtibution of mean arterial pressure stratified by quitting smoking status in the NHEFS data.

Figure 1 shows the distribution of mean arterial pressure in the NHEFS data stratified by quitting smoking status. To make our "controlled direct effect" question more specific, we might ask what the relation between quitting smoking and death by 1992 would be if nobody in the sample had high mean arterial pressure? In effect, what would the relation between quitting smoking and death be if no individuals in the sample had a mean arterial pressure of greater than 100 mm Hg (i.e., high MAP)?

What this means is that the **referent value** to which we want to hold everyone fixed at for the mediator in our controlled direct effect is: `map <= 90`.

So we could construct a binary variable for mean arterial pressure that would take a value of 1 if an individual had a MAP of greater than or equaled to 90, and zero otherwise:

```
nhefs <- nhefs %>%
  mutate(map_binary = as.numeric(map >= 90))

nhefs %>%
  group_by(map_binary) %>%
  summarize(mean_wt_change = mean(map),
            max_wt_change = max(map),
            min_wt_change = min(map))
```

```
## # A tibble: 2 x 4
##   map_binary mean_wt_change max_wt_change min_wt_change
##        <dbl>          <dbl>         <dbl>         <dbl>
## 1          0           83.1          89.7          66.7
## 2          1          101.          150.           90
```

If we revisit our simple DAG, we can begin the process of thinking through what we'll need to adjust for to control confounding. At the very lest, to estimate the controlled direct effect we need to ensure that there is:

- No uncontrolled mediator-outcome confounding
- No uncontrolled exposure-outcome confounding

Additionally, if there are mediator-outcome confounders affected by the exposure, then we need to adjust for these carefully. In this case, it seems that weight change is a variable that confounds the relation between mean arterial pressure and death, and that is also affected by quitting smoking. So we'll use two methods to adjust for this confounding variable carefully.

Other than weight change, the variables in NHEFS that might **confound the relation between MAP and death** include: high blood pressure at baseline, use of high blood pressure medication at baseline, age, sex, race, income, and exercise status.

The variables in NHEFS that might **confound the relation between quitting smoking and death** include: high blood pressure at baseline, use of high blood pressure medication at baseline, age, sex, race, income.

## 1.1 Estimating the Controlled Direct Effect with IP Weighting

With our exposure, mediator, and outcome defined, and our list of confounders identified, we're ready to go ahead and estimate the controlled direct effect in these data. To do this, we'll use IP weighting, which means we'll need to construct inverse probability weights for two variables: the exposure `qsmk` and the mediator `map_binary`. We'll start by constructing a propensity score for quitting smoking, construct stabilized IPWs, and then do the same for `map_binary`:

```
# PS model for quitting smoking: need to include all confounders of exposure-outcome relation
nhefs$ps_qsmk <- glm(qsmk ~ factor(hbp) + factor(hbpmed) + ns(age, df = 4) + sex +
                       race + income + ns(cholesterol, df = 4) + factor(diabetes) +
                       ns(smokeintensity, df = 4) + ns(smokeyrs, df = 4),
                     data = nhefs,
                     family = binomial("logit"))$fitted.values

nhefs$sw_qsmk <- (mean(nhefs$qsmk)/nhefs$ps_qsmk)*nhefs$qsmk +
  (mean(1 - nhefs$qsmk)/(1 - nhefs$ps_qsmk))*(1 - nhefs$qsmk)

summary(nhefs$sw_qsmk)
```

```
##    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
##  0.3232  0.8845  0.9626  0.9989  1.0691  4.8270
```

```
# PS model for map_binary: need to include all confounders of mediator-outcome relation
nhefs$ps_map <- glm(map_binary ~ factor(hbp) + factor(hbpmed) + ns(age, df = 4) + sex +
                      race + income + + ns(cholesterol, df = 4) + factor(diabetes) +
                      ns(smokeintensity, df = 4) + ns(smokeyrs, df = 4) +
                      factor(exercise) + wt_delta ,
                    data = nhefs,
                    family = binomial("logit"))$fitted.values
```

```
nhefs$sw_map <- (mean(nhefs$map_binary)/nhefs$ps_map)*nhefs$map_binary +
  (mean(1 - nhefs$map_binary)/(1 - nhefs$ps_map))*(1 - nhefs$map_binary)

summary(nhefs$sw_map)
```

```
##    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
##  0.4284  0.7919  0.9169  0.9989  1.1023  5.0796
```

```
## let's explore distribution of combined weights
summary(nhefs$sw_qsmk*nhefs$sw_map)
```

```
##    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
##  0.2157  0.7459  0.9040  0.9916  1.1286  4.5401
```

Now that we have our weights, we're ready to estimate the effects that we need. This includes the overall effect of quitting smoking on death, as well as the effect of quitting smoking on death that would be observed if we held mean arterial pressure fixed to less than 100 mm Hg for everyone in the sample:

```
# unadjusted model: quitting smoking and death
mod0 <- lm(death ~ qsmk, data = nhefs)
coeftest(mod0, vcov. = vcovHC)
```

```
##
## t test of coefficients:
##
##             Estimate Std. Error t value Pr(>|t|)
## (Intercept) 0.171818   0.011384 15.0929  < 2e-16 ***
## qsmk        0.047018   0.024612  1.9104  0.05628 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
# adjusted model: quitting smoking and death
mod1 <- lm(death ~ qsmk, data = nhefs, weights = sw_qsmk)
coeftest(mod1, vcov. = vcovHC)
```

```
##
## t test of coefficients:
##
##             Estimate Std. Error t value Pr(>|t|)
## (Intercept) 0.181851   0.012079 15.0552   <2e-16 ***
## qsmk        0.015434   0.026110  0.5911   0.5545
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
# unadjusted model: quitting smoking and death under map_binary = 0
mod2 <- lm(death ~ qsmk + map_binary + qsmk:map_binary, data = nhefs)
coeftest(mod2, vcov. = vcovHC)
```

```
##
## t test of coefficients:
##
##                  Estimate Std. Error t value  Pr(>|t|)
## (Intercept)      0.104019   0.014879  6.9912 4.138e-12 ***
## qsmk             0.101338   0.041289  2.4544   0.01423 *
## map_binary       0.110161   0.021696  5.0775 4.318e-07 ***
## qsmk:map_binary -0.090619   0.051574 -1.7571   0.07911 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
# adjusted model: quitting smoking and death under map_binary = 0
mod3 <- lm(death ~ qsmk + map_binary + qsmk:map_binary, data = nhefs, weights = sw_qsmk*sw_map)
coeftest(mod3, vcov. = vcovHC)
```

```
##
## t test of coefficients:
##
##                  Estimate Std. Error t value  Pr(>|t|)
## (Intercept)      0.128712   0.019788  6.5046 1.068e-10 ***
## qsmk             0.082362   0.048812  1.6873  0.091755 .
## map_binary       0.076914   0.025341  3.0351  0.002447 **
```

```
## qsmk:map_binary -0.073139   0.060466 -1.2096  0.226632
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Now that we've estimated these effects, we can start interpreting them. These results are not what we might expect given what we know about smoking, blood pressure, and death, but we can still interpret them, and possibly identify some reasons as to why we are getting these results.

The first set of results we'll interpret will be the adjusted relationship between quitting smoking and death. The risk difference we estimated for this effect is 1.5 per 100, with 95% sandwich variance confidence intervals of (-3.6, 6.7).

This is basically a null association, but if we were to interpret it exactly, we could say that for every 100 people in the sample, if everyone would quit smoking there would be 1.5 more deaths on average than if everyone were to not quit smoking.

Similarly, for the controlled direct effect estimate, the risk difference is 8.2 per 100, with 95% sandwich variance confidence intervals of (-1.3, 17.8).

But how to we interpret the adjusted controlled direct effect estimate?

This too is basically a null association but, again, to interpret it exactly, we would say that, *in a world were we managed to hold everyone's mean arterial pressure at less than 90 mm Hg,* then for every 100 people in the sample, if everyone would quit smoking there would be 8.2 more deaths on average than if everyone were to not quit smoking.

## 1.2 Assumptions for Causal Inference and Controlled Effects

It's always important to consider the assumptions involved when we estimate effects using data. As we noted above, at the very least, for our controlled direct effect estimate to be valid, we need to assume that there is:

- No uncontrolled mediator-outcome confounding
- No uncontrolled exposure-outcome confounding

One reason why we may have seen null results for our quitting smoking association is that we were missing important confounders for the quitting smoking-death relation. This is important because the NHEFS dataset is a

difficult one to use to answer this question. There are a lot of dimensions of smoking that need to be considered, such as how much a person smokes, how long a person has been smoking, and what the reasons are that motivated them to quit. We tried to address some of this by adjusting for the number of cigarettes smoked per day in 1971 (smokeintensity) and the number of years of smoking (smokeyears), but it is entirely possible that this adjustment just wasn't sufficient. We could, if time permitted, do a more extensive analysis to shed light on the null association between quitting smoking and death, but we have to move on.

Because we used IP weighting, we can appropriately handle the mediator-outcome confounder affected by the exposure. Had we used the difference or product method, we would not have been able to appropriately handle `wt_delta` in the analysis above.

Additionally, to interpret these results as estimates of the "causal effect" of quitting smoking on death, there are a number of additional assumptions that we need. These include things like counterfactual consistency. This assumptions are more believable when the exposure is something that is "manipulable", so that we can conceive of some form of intervention to change the exposure. In the case of quitting smoking, this is the case, and so we might make the case that this assumption holds in our setting. However, such is not usually the case when we do health disparities work.

## 2 Health Disparities Research

In this section, we are going to build off of, or mimick, what we just did above to estimate the controlled direct effect, but this time we will focus on a health disparity question instead.

Before we start though, it will be useful to ask: What is a Disparity? More specifically, what's the difference between a measure of effect, such as:

- the estimated effect of quitting smoking on death?

versus a measure of "disparity", such as:

- the estimated racial disparity in weight change between 1971 and 1982?

The answer to this question has important implications for precisely **how** we might go about conducting this analysis. For example, in the analysis

quantifying the effect of quitting smoking on death, and the controlled direct effect that we'd obtain if everyone's MAP was fixed at < 90 mm Hg, we had to adjust for confounding of the exposure-outcome association.

Confounding is a causal concept. That is, an **association** between an exposure and outcome may not reflect the **causal effect** of the exposure on the outcome because of bias due to confounding. For this reason, we have to carefully balance the interpretation of points estimates for an exposure-outcome association as causal effects with whether the assumptions required for our causal interpretation to be valid hold.

If, on the balance, we believe our assumptions hold, then we can justify interpreting estimates causally. This would allow us to state things like, "the risk of death that would be observed if everyone quit smoking, versus the risk of death that would be observed if no one quit smoking."

However, this is not the case for disparities. There is little to no interest in asking what the risk of some outcome would be if everyone's racial status were set to "non-Hispanic Black" versus if everyone's racial status were set to "non-Hispanic White." Why? Because measures such as self-reported race are extremely complex constructs that involve issue of structural and interpersonal racism, social, political, and economic factors, as well as cultural and historic factors.

For this reason, it seems less sensible to ask questions about what would happen if we managed to "set" someone's racial status to some value. Doing this ignores the complexity of constructs such as race.

## 2.1 The Problem of "Fundamental Causes"

This issue is furthermore not specific to only race. Nearly every exposure of interest in social epidemiology and the study of health disparities is characterized by similar issues. Examples include socioeconomic status, wealth, occupation, certain neighborhood characteristics, as well as a host of other constructs of interest.

The common feature of all of these, I believe, is the fact that they represent what Link and Phelan referred to in 1995 as "fundamental causes" (Link and Phelan, 1995). Exposures such as race, socioeconomic status, and other markers of disparity that rely on complex sociological processes that unfold over generations undoubtedly shape the risk of health outcomes. However, it

would not make sense to try to quantify the risk of these outcomes that would be observed if we switched the value of one fundamental cause to another value.

## 2.2 A Way Forward

So how can we analyze health disparities data in a way that avoids simply stating the obvious: that disparities in some outcome are present or not?

First, we should articulate what a disparity measure is. Next, once we've done that, we can proceed to use mediation methods to start disentangling the role that potential "intermediary" variables play in perpetuating a disparity.

The first point is important because it has practical implications. For example, if we agree that a disparity measure is simply a measure of association or difference between a "fundamental cause" and a health outcome, this suggests that we need not worry about adjusting our health disparity measure for too many variables, if we choose to adjust at all.

For example, we can estimate the disparity in quitting smoking by race in the NHEFS data in a number of ways:

```
file_loc <- url("https://is.gd/VPKKsi")
nhefs <- read_csv(file_loc) %>%
  mutate(map = dbp + (sbp - dbp)/3) %>%
  select(qsmk, map, wt82_71, death, hbp, smokeintensity,
         smokeyrs, hbpmed, age, race, sex, income,
         exercise, cholesterol, diabetes) %>%
  na.omit()

mod1 <- lm(qsmk ~ race, data = nhefs)

res1 <- coeftest(mod1, vcov. = vcovHC)

res1
```

```
##
## t test of coefficients:
##
```

```
##              Estimate Std. Error t value  Pr(>|t|)
## (Intercept)  0.260425   0.012320 21.1388 < 2.2e-16 ***
## race        -0.102530   0.029309 -3.4983 0.0004824 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

This suggests that, on average, for every 100 individuals in the population, 10 fewer "black or other" individuals in the NHEFS data quit smoking between 1971 and 1982 relative to those labeled as "white".

An important question is: should this association be adjusted for anything? My view is generally "no", with certain exceptions. For example, we may want to standardize this risk difference to the age distribution in some population. However, outside of this rationale, my view is that we should avoid adjusting disparity measures such as this risk difference for too many variables.[1]

[1] It is, however, important to note that there is room for disagreement and discussion here.

With that being said, let's now conduct a mediation analysis to compute disparity measures with the NHEFS data.

## 2.3 Measuring Disparities under Counterfactual Scenarios

Let's say we're interested in the relation between race, quitting smoking, and weight change in the NHEFS data. Specifically, we might be interested in answering this specific question:

What would the magnitude of the racial disparity in weight change between 1971 and 1982 be if everyone in the NHEFS data were to quit smoking?

We can use the same mediation methods that we implemented above to answer this question, with some minor modifications. First, let's draw a diagram that will help us think through what to adjust for and how in this scenario:

## 2.4 Estimating the Counterfactual Disparity Measures with IP Weighting

Based on this diagram, we know that we can't use the difference or product methods. Let's use IP weighting again. As we did above, we first have to code our variables accordingly. Here, we want to estimate the disparity in weight change that would remain if **everybody quit smoking**. Because of this, we need to ensure that the **referent level** for our quit smoking variable is "quit smoking". At present, this is not currently the case (per the NHEFS Codebook).

So we'll modify our quit smoking variable as follows:

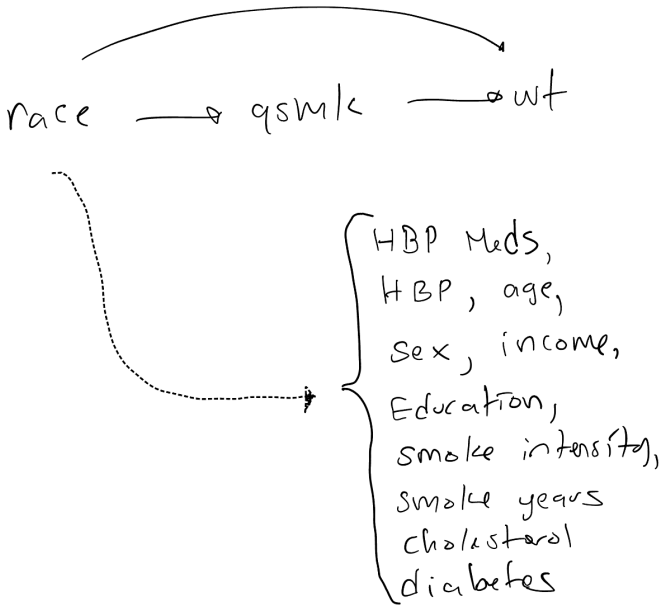


Figure 3: Diagram depicting relations between race, quitting smoking, weight change, and a host of variables to be adjusted for.

```
nhefs <- nhefs %>%
  mutate(qsmk = 1 - qsmk)
```

Again, with our exposure (race), mediator (qskm), and outcome (wt82_71) defined, and our list of confounders identified from the diagram above, we're ready to go ahead and estimate the quantity we want in these data. Methodologically, this quantity can be computed in almost the same way as the controlled direct effect. But interpretationally, this quantity is different from the controlled direct effect. For this reason, I referred to this quantity in the past as the "counterfactual disparity measure" (Naimi et al., 2016). This quantity is a disparity measure, because it measures the association between the exposure (race) and the outcome (weight change). However, it is "counterfactual" because it measures this association in a hypothetical (counterfactual) world were we intervene on the mediator (in this case, setting everybody to "quit smoking").

We'll again use IP weighting. Because we are not interested in adjusting for anything in the association between race and weight change, we do not need to construct weights for race. But we will have to construct weights for our quitting smoking variable:

```r
# PS model for race: fitting intercept only, which is equivalent to not adjusting for anything
nhefs$ps_race <- glm(race ~ 1,
                     data = nhefs,
                     family = binomial("logit"))$fitted.values

nhefs$sw_race <- (mean(nhefs$race)/nhefs$ps_race)*nhefs$race +
  (mean(1 - nhefs$race)/(1 - nhefs$ps_race))*(1 - nhefs$race)

summary(nhefs$sw_race)
```

```
##    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
##       1       1       1       1       1       1
```

```r
# PS model for qsmk: need to include all confounders of mediator-outcome relation
# NB: it does not matter that we switched the coding for this variable
nhefs$ps_qsmk <- glm(qsmk ~ factor(hbp) + factor(hbpmed) + ns(age, df = 4) + sex +
                      race + income + + ns(cholesterol, df = 4) + factor(diabetes) +
                      ns(smokeintensity, df = 4) + ns(smokeyrs, df = 4) +
                      factor(exercise),
                     data = nhefs,
                     family = binomial("logit"))$fitted.values

nhefs$sw_qsmk <- (mean(nhefs$qsmk)/nhefs$ps_qsmk)*nhefs$qsmk +
  (mean(1 - nhefs$qsmk)/(1 - nhefs$ps_qsmk))*(1 - nhefs$qsmk)

summary(nhefs$sw_qsmk)
```

```
##    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
##  0.3361  0.8779  0.9612  0.9985  1.0681  4.7446
```

```r
## let's explore distribution of combined weights
summary(nhefs$sw_race*nhefs$sw_qsmk)
```

```
##    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
##  0.3361  0.8779  0.9612  0.9985  1.0681  4.7446
```

Now that we have our weights, we're ready to estimate the effects that we need:

```
# adjusted model: quitting smoking and death
mod1 <- lm(wt82_71 ~ race, data = nhefs)
coeftest(mod1, vcov. = vcovHC)
```

```
##
## t test of coefficients:
##
##             Estimate Std. Error t value Pr(>|t|)
## (Intercept)  2.63666    0.21709 12.1456   <2e-16 ***
## race        -0.29006    0.66564 -0.4358   0.6631
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
# adjusted model: quitting smoking and death under map_binary = 0
mod2 <- lm(death ~ race + qsmk + race:qsmk, data = nhefs, weights = sw_qsmk)
coeftest(mod2, vcov. = vcovHC)
```

```
##
## t test of coefficients:
##
##               Estimate Std. Error t value Pr(>|t|)
## (Intercept)  0.1820671  0.0215576  8.4456   <2e-16 ***
## race         0.1029550  0.1048275  0.9821   0.3262
## qsmk        -0.0037522  0.0251642 -0.1491   0.8815
## race:qsmk   -0.0771843  0.1106718 -0.6974   0.4857
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Let's interpret these results. The first set we'll interpret is the overall association between race and weight change. The mean difference we estimated for this effect is -0.29, with 95% sandwich variance confidence intervals of (-1.59, 1.01). This suggests that, on average, the difference in weight between 1971 and 1982 is -0.29 kilograms lower among those who identify as "black or other" versus those who identify as "white."[2]

[2] Note: the NHEFS codebook does not clarify whether this is self or other (e.g., physician) identification.

Now we might as what would happen to this mean difference if everyone quit smoking? To answer this, we can read off the point estimate from the second model. This tells us that, if all individuals in the NHEFS were to quit smoking, the mean difference would be 0.103, with 95% sandwich variance confidence intervals of (-0.1, 0.31). This suggests that, on average, the difference in weight between 1971 and 1982 that would be observed if everyone quit smoking is 0.103 kilograms lower among those who identify as “black or other” versus those who identify as “white.”

## References

B G Link and J Phelan. Social conditions as fundamental causes of disease. *J Health Soc Behav*, 35((Extra Issue)):80–94, 1995.

Ashley I. Naimi, Mireille E. Schnitzer, Erica E. M. Moodie, and Lisa M. Bodnar. Mediation analysis for health disparities research. *American Journal of Epidemiology*, 184(4):315–324, 2016. DOI: 10.1093/aje/kwv329. URL http://aje.oxfordjournals.org/content/184/4/315.abstract.