Mediation Analysis

The purpose of this exercise is to develop data visualization techniques to illustrate that one variable is a mediator for a treatment effect and that this mediator effect is stronger than in other variables.

Data description

The data was simulated based on a parallel study design studying a treatment vs placebo. Treatment variable, TRT, is encoded as "Rx" for the experimental treatment and "placebo" for placebo. There were 120 patients randomized to each arm. The endpoint of interest is a patient reported outcome, $DLQI$, at 24 weeks. $DLQI$ ranges from $0, ..., 30$, the lower score the better. Possible mediator variables are:

- *itch*: Patient self report this measure every day in a diary. The measurements range from $0, ..., 10$ and are averaged every week to give a weekly measure. The lower the score the better. The average of the measurements taken the week prior to week 24 is provided in this data set.
- *redness*: Patient self report this measure every day in a diary. The measurements range from $0, ..., 10$ and are averaged every week to give a weekly measure. The lower the score the better. The average of the measurements taken the week prior to week 24 is provided in this data set.
- BSA: Measured by the physician at each visit. The measurements range from $0, ..., 100\%$. The lower the score, the better. The body surface area reported at week 24 is provided in this data set.

Missing data was imputed using Last Observation Carried Forward, $LOCF$. A logical flag column for each of the data columns is included in this data set using the naming convention $< variable > \_LOCF$. A summary of the imputed data for each of the variables is given below.

```
##         itch (%) BSA (%) redness (%) DLQI (%)
## placebo       28      28          28       28
## Rx            14       6          14       14
```

All analyses was done using the $LOCF$ imputed data.

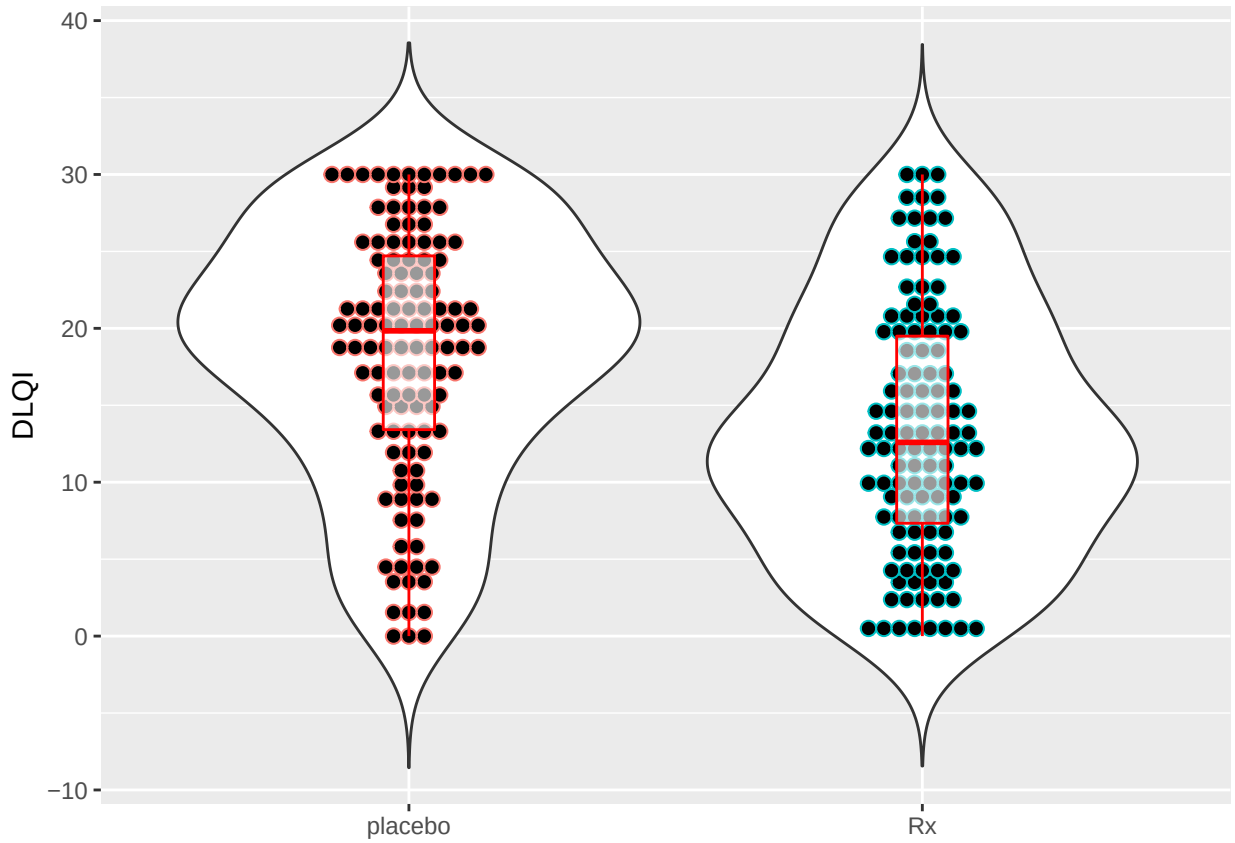
Step 1

We first establish that there is a treatment effect. We regress the dependent variable, $DLQI$, on the independent variable, TRT, to confirm that the independent variable is a significant predictor of the dependent variable.

Plot DLQI vs TRT

```
## Registered S3 methods overwritten by 'ggplot2':
##   method         from
##   [.quosures     rlang
##   c.quosures     rlang
##   print.quosures rlang
```

```
## `stat_bindot()` using `bins = 30`. Pick better value with `binwidth`.
```



$$DLQI = \beta_{10} + \beta_{11} \cdot TRT + \epsilon_1$$

```
##
## Call:
## lm(formula = DLQI ~ as.factor(TRT), data = sim.dat)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -18.3338  -5.5686   0.2417   6.3428  16.6317
##
## Coefficients:
##                   Estimate Std. Error t value Pr(>|t|)
## (Intercept)        18.3338     0.7486   24.49  < 2e-16 ***
## as.factor(TRT)Rx  -4.9655     1.0587   -4.69  4.6e-06 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 8.201 on 238 degrees of freedom
## Multiple R-squared:  0.08461,    Adjusted R-squared:  0.08076
## F-statistic:    22 on 1 and 238 DF,  p-value: 4.603e-06
```

```
t.test(DLQI ~ as.factor(TRT), data=sim.dat)
```

```
##
##  Welch Two Sample t-test
##
## data:  DLQI by as.factor(TRT)
```

```
## t = 4.6902, df = 237.96, p-value = 4.604e-06
## alternative hypothesis: true difference in means is not equal to 0
## 95 percent confidence interval:
##  2.879852 7.051111
## sample estimates:
## mean in group placebo      mean in group Rx
##              18.33376              13.36828
```

We confirm that the treatment, β_{11} had a significant effect on DLQI at week 24. Now let's explore the 3 other possible covariates ($itch$, $redness$, BSA) as having a possible mediation effect. Let's start with $itch$.

Itch

Following the mediation approach outlined by Baron and Kenny (1986), we regress $itch$ on the treatment to confirm that the treatment, TRT, is a significant predictor of the mediator variable candidate, $itch$.

Step 2

$$itch = \beta_{20} + \beta_{21} \cdot TRT + \epsilon_2$$

```
##
## Call:
## lm(formula = itch ~ TRT, data = sim.dat)
##
## Residuals:
##    Min     1Q Median     3Q    Max
## -5.918 -2.042 -0.049  2.047  5.385
##
## Coefficients:
##             Estimate Std. Error t value Pr(>|t|)
## (Intercept)   5.9249     0.2320  25.537  < 2e-16 ***
## TRTRx        -1.4367     0.3281  -4.379 1.79e-05 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 2.542 on 238 degrees of freedom
## Multiple R-squared:  0.07455,    Adjusted R-squared:  0.07066
## F-statistic: 19.17 on 1 and 238 DF,  p-value: 1.789e-05
```

We see that β_{21} is significant. This confirms the second step of the mediation analysis, that the treatment, TRT, is a signficant predictor of the mediator variable candidate, $itch$.

Now we go to the next step, and regress $DLQI$ on TRT and $itch$

Step 3

$$DLQI = \beta_{30} + \beta_{31} \cdot TRT + \beta_{32} \cdot itch + \epsilon_3$$

```
##
## Call:
## lm(formula = DLQI ~ TRT + itch, data = sim.dat)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
```

```
## -11.5056  -2.9592   0.0089   3.2170  12.6048
##
## Coefficients:
##             Estimate Std. Error t value Pr(>|t|)
## (Intercept)   2.5368     0.8172   3.104  0.00214 **
## TRTRx        -1.1350     0.6212  -1.827  0.06892 .
## itch          2.6662     0.1181  22.585  < 2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 4.629 on 237 degrees of freedom
## Multiple R-squared:  0.7096, Adjusted R-squared:  0.7072
## F-statistic: 289.6 on 2 and 237 DF,  p-value: < 2.2e-16
```

We see that β_{32} is signficant and β_{31} is smaller in absolute value than the original treatment effect (β_{11} above). This allows us to infer that *itch* has a mediation effect on the treatment effect on $DLQI$. Now let's investigate BSA.

BSA

Step 2

Following the mediation approach outlined by Baron and Kenny (1986), we regress BSA on the treatment to confirm that the treatment, TRT, is a significant predictor of the mediator variable candidate, BSA.

$$BSA = \beta_{20} + \beta_{21} TRT + \epsilon_2$$

```
##
## Call:
## lm(formula = BSA ~ TRT, data = sim.dat)
##
## Residuals:
##     Min      1Q  Median      3Q     Max
## -40.760  -9.914   0.790  10.730  36.157
##
## Coefficients:
##             Estimate Std. Error t value Pr(>|t|)
## (Intercept)   81.030      1.371   59.12   <2e-16 ***
## TRTRx        -39.754      1.939  -20.51   <2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 15.02 on 238 degrees of freedom
## Multiple R-squared:  0.6386, Adjusted R-squared:  0.6371
## F-statistic: 420.6 on 1 and 238 DF,  p-value: < 2.2e-16
```

We see that β_{21} is significant. This confirms the second step of the mediation analysis, that the treatment, TRT, is a signficant predictor of the mediator variable candidate, BSA.

Now we go to the next step, an regress $DLQI$ on TRT and BSA

Step 3

$$DLQI = \beta_{30} + \beta_{31} \cdot TRT + \beta_{32} \cdot BSA + \epsilon_3$$

```
##
## Call:
## lm(formula = DLQI ~ TRT + BSA, data = sim.dat)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -18.2216  -5.6955   0.2558   6.3063  17.3388
##
## Coefficients:
##             Estimate Std. Error t value Pr(>|t|)
## (Intercept) 21.66189    2.96250   7.312 4.03e-12 ***
## TRTRx       -6.59828    1.75981  -3.749 0.000223 ***
## BSA         -0.04107    0.03538  -1.161 0.246791
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 8.195 on 237 degrees of freedom
## Multiple R-squared:  0.08978,    Adjusted R-squared:  0.0821
## F-statistic: 11.69 on 2 and 237 DF,  p-value: 1.441e-05
```

From this analysis we see that when conditioned on TRT, BSA is no longer a significant predictor of $DLQI$. There is no evidence from this data that BSA mediates the treatment effect on $DLQI$.

redness

Now lets examine the potential of *redness* to mediate the treatment effect on $DLQI$.

Step 2

Following the mediation approach outlined by Baron and Kenny (1986), we regress *redness* on the treatment to confirm that the treatment, TRT, is a significant predictor of the mediator variable candidate, *redness*.

$$redness = \beta_{20} + \beta_{21} \cdot TRT + \epsilon_2$$

```
##
## Call:
## lm(formula = redness ~ TRT, data = sim.dat)
##
## Residuals:
##     Min      1Q  Median      3Q     Max
## -3.9185 -1.0725 -0.0135  1.1185  3.1397
##
## Coefficients:
##             Estimate Std. Error t value Pr(>|t|)
## (Intercept)   7.9889     0.1318   60.62   <2e-16 ***
## TRTRx        -3.5343     0.1864  -18.96   <2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 1.444 on 238 degrees of freedom
## Multiple R-squared:  0.6018, Adjusted R-squared:  0.6001
## F-statistic: 359.7 on 1 and 238 DF,  p-value: < 2.2e-16
```

We see that β_{21} is significant. This confirms the second step of the mediation analysis, that the treatment, TRT, is a signficant predictor of the mediator variable candidate, BSA.

Now we go to the next step, an regress $DLQI$ on TRT and *redness*

Step 3

$$DLQI = \beta_{30} + \beta_{31} \cdot TRT + \beta_{32} \cdot redness + \epsilon_3$$

```
##
## Call:
## lm(formula = DLQI ~ TRT + redness, data = sim.dat)
##
## Residuals:
##     Min      1Q  Median      3Q     Max
## -18.895  -5.806   0.122   6.278  17.640
##
## Coefficients:
##             Estimate Std. Error t value Pr(>|t|)
## (Intercept)  22.0677     3.0317   7.279 4.92e-12 ***
## TRTRx        -6.6174     1.6755  -3.949 0.000103 ***
## redness      -0.4674     0.3678  -1.271 0.205011
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 8.19 on 237 degrees of freedom
## Multiple R-squared:  0.0908, Adjusted R-squared:  0.08313
## F-statistic: 11.83 on 2 and 237 DF,  p-value: 1.262e-05
```

From this analysis we see that when conditioned on TRT, *redness* is no longer a significant predictor of $DLQI$. There is no evidence from this data that *redness* mediates the treatment effect on $DLQI$.

Examine regression model with all 3 covariates plus TRT

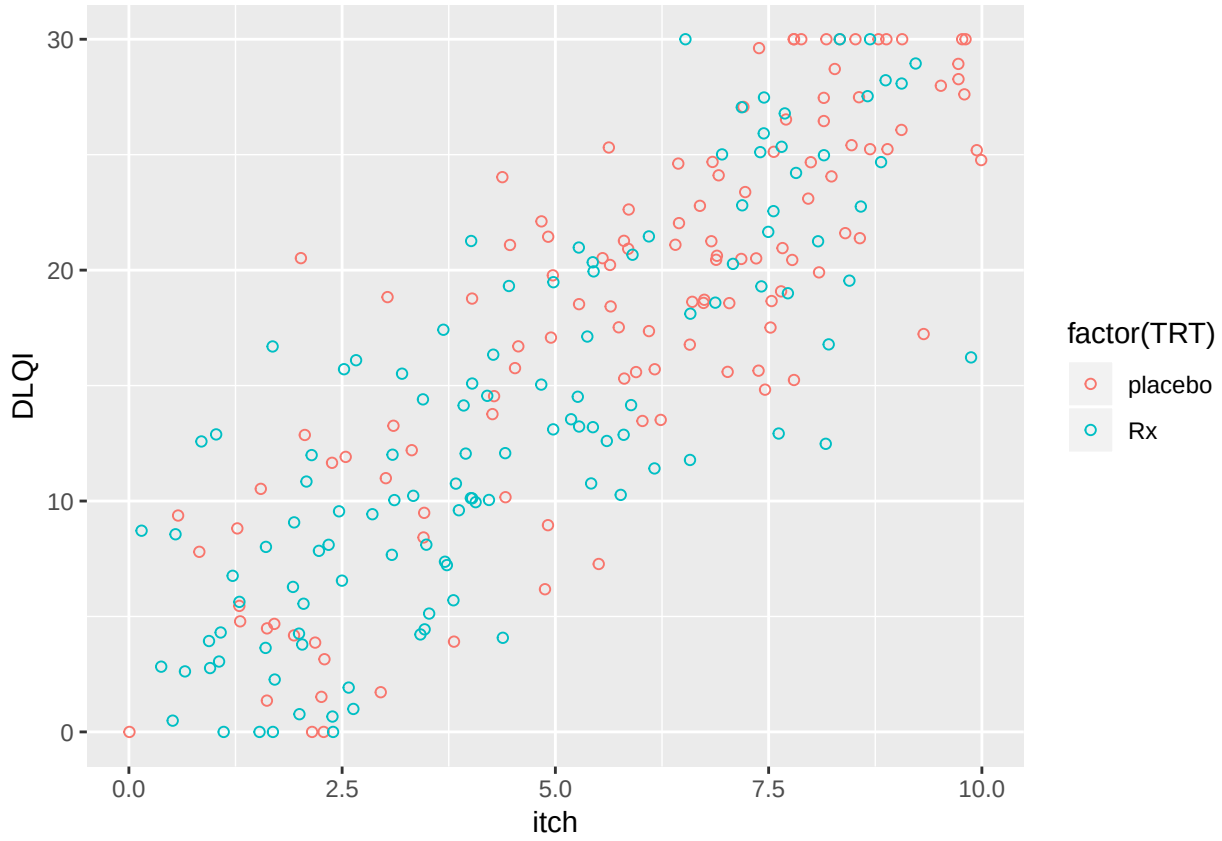
When we consider all 3 covariates and treatment together, *itch* is the only significant predictor of DLQI.

```
##
## Call:
## lm(formula = DLQI ~ TRT + redness + itch + BSA, data = sim.dat)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -11.4515  -3.2002  -0.0125   3.2950  12.7668
##
## Coefficients:
##             Estimate Std. Error t value Pr(>|t|)
## (Intercept)  5.37137    2.42477   2.215   0.0277 *
## TRTRx       -2.41669    1.22323  -1.976   0.0494 *
## redness     -0.24400    0.20894  -1.168   0.2441
## itch         2.65601    0.11846  22.421   <2e-16 ***
## BSA         -0.01018    0.02011  -0.506   0.6132
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 4.631 on 235 degrees of freedom
```

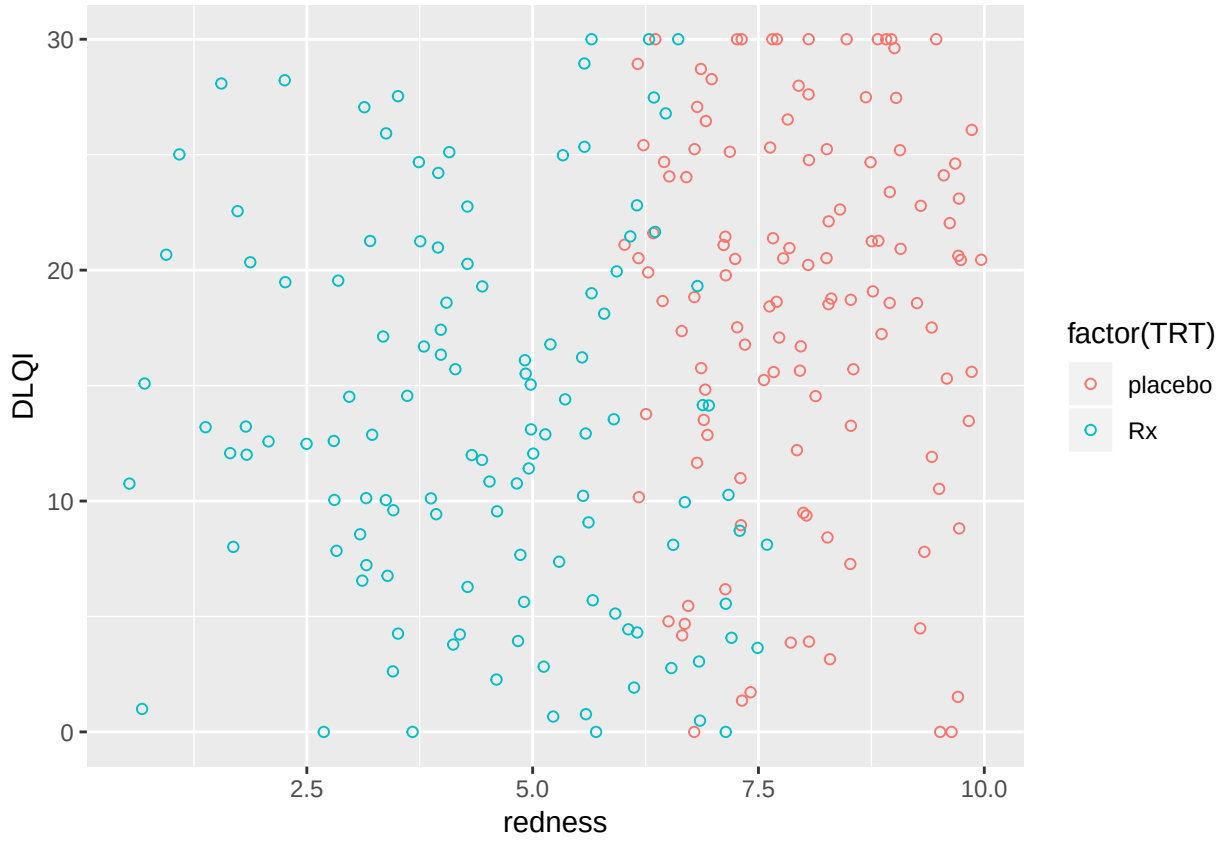
```
## Multiple R-squared:  0.7117, Adjusted R-squared:  0.7068
## F-statistic: 145.1 on 4 and 235 DF,  p-value: < 2.2e-16
```

Plot the data

Below are plots of the imputed data set.


30
20
10
0
DLQI
0.0
2.5
5.0
7.5
10.0
itch
factor(TRT)
placebo
Rx


30
20
10
0
DLQI
0
25
50
75
100
BSA
factor(TRT)
placebo
Rx



Goals of the data viz

The target audience for this data viz are prescribing physicians and thought leaders in dermatology. The data viz is for 'explanatory' purposes (not 'exploratory'). The story is that *treatment* is superior to placebo in terms of patient reported outcomes, $DLQI$. The treatment effect is mediated by it's effect on *itch*. (The reason why *treatment* improved $DLQI$ so much is due to it's improvement on *itch* which directly improves $DLQI$.) And, moreover, the other variables considered, *redness* and BSA, do not mediate the treatment effect on $DLQI$. We want to tell this story in a compelling way that is visually appealing.

Other things to consider, the clinically meaningful $DLQI$ value is 5. (A patient who has a score greater than 10 is considered to have been impacted seriously by the disease.) A clinically relevant threshold for *itch* is 4. (A patient with an itch score greater than 4 is considered to be suffering greatly.) A clinically meaningful threshold for BSA is 10% and a clinically meaningful value for *redness* is 4. (A BSA value greater than 50% or a *redness* score greater then 4 is considered clinically meaningful.)

Take into account the missing data in your data viz. Let readers understand the nuances of the data as well as the message. Our objective is to be objective. We want to be transparent with the data in addition to conveying our insights into the data in a concise way.