Causal inference: how to analyse causal scenarios correctly, and repercusions of a wrong analysis

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Contents

1 Objective

Causal inference is a key element in statistics. It help us reach valuable conclusions about how do variables relate to one another, and help us make decisions in order to mantain our health, combat disease, adjust habits, etc. The problem comes when data is misinterpreted, and correlation is mistaken by causalty. It is very different to say 'ice cream causes cancer' rather than 'in the same season of the year, both ice cream sales and number of melanoma diagnosis increase'. A wrong conclusion can have serious repercusions, that may go from administrating a wrong treatment to ruining the ice cream economy. Even if our field of study is not statistics, it is interesting to understand some basic concepts to prevent us from being fooled by sensational news and develop the so called 'critical thinking'. The objective of this project is to show what changes when data is modelled in the wrong way and how to interpret it correctly. The code can be accessed from the GitHub repository Causalinference - GitHub repository . We recommend to get the code from it, as some updates may not be reflected in this file. Along the document, we will explain basic concepts with examples, vaguely based in real life events. It is present all the code necessary to perform each of the cases.

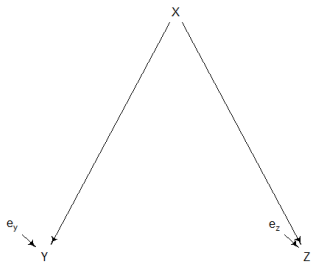
2 What to do when there is a common cause

In this section, we will cover the difficulties that may come when we want to analyse the cause of an outcome variable, Z, when it is affected by X. X is a variable that doesn't only affect Z, but also a second variable, Y: for this reason, X is a **common cause** of both X and Y. We have used the following modules to make the analysis:

```
library(dagitty)
library(car)
library(rethinking)
if(!suppressWarnings(require("rethinking",
quietly = TRUE))) {drawdag <- plot}
```

The variable Y can have an effect on X or not. This gives us two basic scenarios to work on. The first scenario is illustrated in the following DAG:

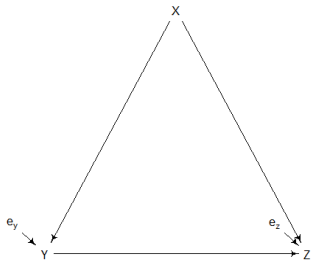
```
scenario1.DAG <- dagitty("dag {
X -> Y
X -> Z
e_y -> Y
e_z -> Z
}")

coordinates(scenario1.DAG) <- list(x = c(Y = 1, X = 2, Z
    = 3, e_y = 0.75, e_z = 2.75), y = c(Y = 3, X = 1, Z =
    3, e_y = 2.75, e_z = 2.75))

drawdag(scenario1.DAG)
```



In this first case, Y is not related to Z. The second scenario would be:

```
scenario2.DAG <- dagitty("dag {
X -> Y
X -> Z
```

```
Y -> Z
e_y -> Y
e_z -> Z}")
coordinates(scenario2.DAG) <- list(x = c(Y = 1, X = 2, Z
    = 3, e_y = 0.75, e_z = 2.75), y = c(Y = 3, X = 1, Z =
    3, e_y = 2.75, e_z = 2.75))
drawdag(scenario2.DAG)
```



In this second case, Y does have an effect over Z. It is important to tell the difference between both of them, as the correct model to apply will be different. How can we tell if our data corresponds to one scenario or another? First of all, we have to address one key problem: **how do we simulate data?** To simulate data in different scenarios, we have used two options: vectors and a function to create datsets. To use vectors is a quick method and very versatile, but if you need to change the coefficients that relate one variable to another it is necessary to create new vectors. Meanwhile, to have a function that creates data frames is useful to make different trials in which the relation between variables is maintained and the coefficients change: the main disadvantage of this method is that anytime the structure of the DAG changes, the function is no longer valid. Both methods are valuable, and each has its advantages and disadvantages. We will use data frames in this chapter and vectors in the next one to show different ways to simulate the data. This first function to create dataframes creates three columns: X, Y and Z. We can change the parameters that relate one varaible to another: if the estimate that multiplies Y for Z is 0, we are representing the scenario 1.

```
create.dataset <- function(b_yz, N = 500, b_xy = 3, b_xz
    = 3,
                                e_x = 1, e_y = 1, e_z = 1) {
  name_df <- data.frame(X = runif(N, 1, 100) + rnorm(N,
      sd = e_x))
  name_df$Y <- name_df$X * b_xy + rnorm(N, sd = e_y)
  name_df$Z <- name_df$X * b_xz + name_df$Y * b_yz +
      rnorm(N, sd = e_z)
```

```
  return(name_df)}
Ynoinfluences <- create.dataset(0)
Yinfluences <- create.dataset(-2)
non.influences <- create.dataset(0, b_xz = 0)
```

Once this is introduce, we can go over the issue that matters. How do we know if our data belongs to scenario 1 or scenario 2?

```
Y_check <- function (dataset, conflevel = 0.01) {
  colnames(dataset) <- c('X','Y','Z')
  model_with_Y <- lm(Z~X+Y, data = dataset)
  p.v.X <-(summary(model_with_Y)$coefficients['X','Pr(>|t
      |)'])
  p.v.Y <- (summary(model_with_Y)$coefficients['Y', 'Pr
      (>|t|)'])

  if ((p.v.X <= conflevel)&(p.v.Y > conflevel))
  {cat("The variable of analysis is not influenced by Y\n
      ")
    cat('See plot\n')
    scenario1.DAG <- dagitty("dag {
    X -> Y
    X -> Z
    e_y -> Y
    e_z -> Z}")
    coordinates(scenario1.DAG) <- list(x = c(Y = 1, X =
        2, Z = 3, e_y = 0.75, e_z = 2.75),y = c(Y = 3, X =
         1, Z = 3, e_y = 2.75, e_z = 2.75))
    drawdag(scenario1.DAG)
    return(invisible(1))}

  if ((p.v.X <= conflevel)&(p.v.Y <= conflevel))
  {cat("The variable of analysis is influenced by both X
      and Y\n")
    cat('See plot\n')
    scenario2.DAG <- dagitty("dag {
    X -> Y
    X -> Z
    Y -> Z
    e_y -> Y
    e_z -> Z}")
    coordinates(scenario2.DAG) <- list(x = c(Y = 1, X =
        2, Z = 3, e_y = 0.75, e_z = 2.75),y = c(Y = 3, X =
         1, Z = 3, e_y = 2.75, e_z = 2.75))
    drawdag(scenario2.DAG)
    return(invisible(2))}
```

```
  if ((p.v.X > conflevel)&(p.v.Y > conflevel))
  {cat("It seems that neither X or Y affect Z\nYou may
      want to review your working model\n")
  return(invisible(0))}

  if ((p.v.Y <= conflevel)&(p.v.X > conflevel))
  {cat('It looks like Y is related to Z, but not Z\nYou
      may want to revisit the hypothesis \'X = common
      cause of Y and Z\'')
  return(invisible(0))}
  }
```

An example of its use is:

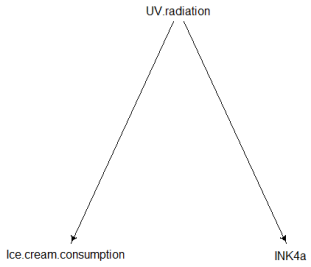
```
a <- Y_check(non.influences)

## It seems that neither X or Y affect Z
## You may want to review your working model

b <- Y_check(Yinfluences)

##The variable of analysis is influenced by both X and Y
##See plot (scenario2 DAG)
```

This function could be optimized in multiple ways, but it shows that the p value of the linear model can be used to classify a data set in one scenario or another. It is necessary to have an idea beforehand of which variable may be the common cause. If by mistake Y is actually the common cause, and X is the mediator, the function wouldn't notice it because **this couldn't be done by p-values**. This concept, of knowing the 'structure of the DAG' or how variables are related, is crucial in causal inference, and has to be based in real facts. It is similar to which came first, the hen or the egg? Which came first, the melanoma or the exposure to UV radiation?

We will now present a example to illustrate the problems of a bad modeling of scenario 1. We will study the expression of gene INK4a, key for melanoma development. It will be the outcome variable, Z. It is directly affected by UV radiation, X. UV radiation can come from sunbathing, which increases the appetite for ice cream consumption, measured in ml of consumed ice cream, Y. You collect data of potentially cancerous tissue from 100 people, from which you know the hours they have spent in the sun the last year, the amount of consumed ice cream and the expression of INK4a.

```
# Theoretical coefficeints between variables
b_xy_i_uv_i <- 5
b_xz_i_uv_i <- 10
b_yz_i_uv_i <- 0
samplesize <- 100
```

```
i_uv_i.DAG <- dagitty("dag {
UV.radiation -> Ice.cream.consumption
UV.radiation -> INK4a}")
coordinates(i_uv_i.DAG) <- list(x = c(Ice.cream.
    consumption = 1, UV.radiation = 2, INK4a = 3),y = c(
    Ice.cream.consumption = 3, UV.radiation = 1, INK4a =
    3))

drawdag(i_uv_i.DAG)
```




```
sc1.comm <- function(b_yz, N, b_xz, b_xy, reps = 100,
    ...){
  onlyY_pv <- rep(NA, reps)
  both_pv <- rep(NA,reps)
  onlyX_coefX <- rep(NA,reps)
  both_coefX <- rep(NA, reps)

  for (i in 1:reps) {
    dataset <- create.dataset(b_yz, N = N, b_xz = b_xz, b
        _xy = b_xy, ...)

    both <- lm(Z~X+Y, data = dataset)
    onlyY <- lm(Z~Y, data = dataset)
    onlyX <- lm(Z~X, data = dataset)
    onlyY_pv[i] <- summary(onlyY)$coefficients["Y", "Pr
        (>|t|)"]
    both_pv[i] <- summary(both)$coefficients["Y", "Pr(>|t
        |)"]

    onlyX_coefX[i] <- summary(onlyX)$coefficients["X", "
        Estimate"]
    both_coefX[i] <- summary(both)$coefficients["X", "
        Estimate"]
    rm(dataset)}
```

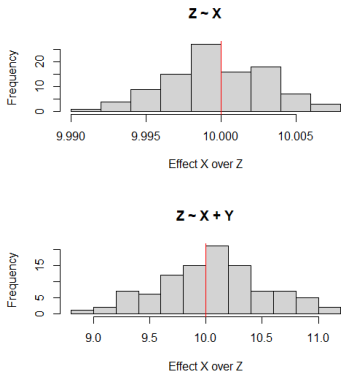
```
  cat('\n Change in relevance of Y on Z\n')
  cat('\nWhen Z ~ Y: \nThe p value of Y is ', mean(onlyY_
      pv),'\n')
  cat('\nWhen Z ~Y + X: \nThe p value of Y is ', mean(
      both_pv), '\n')
  cat('\n Change in effect of X over Z')
  cat('\nWhen Z ~ X: \nThe estimate for X is ', mean(
      onlyX_coefX),'and its s.d. is', sd(onlyX_coefX),'\n'
      )
  cat('\nWhen Z ~Y + X: \nThe estimate for X is ', mean(
      both_coefX),
       'and its s.d. is', sd(both_coefX),'\n')
  cat('\nBeing input x -> z: ', b_xz)
  #This illustrates how, even if the estimate of the
      coefficient for X is similar in both cases, the
      variance is higher in the presence of Y
  op <- par(mfrow= c(2,1), mar = rep(3,4))
  hist(onlyX_coefX, main = 'Z ~ X', xlab = 'Effect X over
       Z')
  abline(v = b_xz, col = 'red')
  hist(both_coefX, main = 'Z ~ X + Y', xlab = 'Effect X
      over Z')
  abline(v = b_xz, col = 'red')
  par(op)}
```

If we call this function with the data for this particular case, this is the output:

```
sc1.comm(b_yz = b_yz_i_uv_i, N = samplesize, b_xz = b_xz_
    i_uv_i, b_xy = b_xy_i_uv_i)
```

```
## Change in relevance of Y on Z
## When Z ~ Y:
## The p value of Y is  1.888825e-202
## When Z ~Y + X:
## The p value of Y is  0.5211384
## Change in effect of X over Z
## When Z ~ X:
## The estimate for X is  10.00005 and its s.d. is
    0.003373088
## When Z ~Y + X:
## The estimate for X is  9.982808 and its s.d. is
    0.444773
## Being input x -> z:  10
```

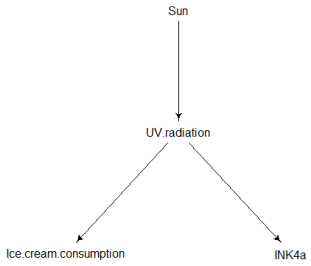
As can be seen, Y is only relevant when we are not condicioning on X. This means that if we condition on ice cream sales but not on UV radiation, we



will see association with INK4a. This association is not causation, but if it is mistaken, will result in a quite silly conclusion.

```
impliedConditionalIndependencies(i_uv_i.DAG)
## INK4 _||_ Ic.. | UV.r
\begin{lstlisting}

On the other hand, we see that the calculated coefficient
    for X, thus, UV radiation, is quite similar to the
    input estimate in both models. What is interesting to
    see is that the variance of the estimate increases
    when conditioning on Y.
In this type of situation, it is not advised to condition
    on Y, ice cream, because it won't give more
    information about melanoma and INK4a and will affect
    negatively to our estimate of UV radiation, that is a
    more interesting variable to study. It is important to
    condition on UV radiation, which is called a \textbf{
    confounder}.
One interesting variation of scenario 1, among all
    variations that can be done, is if there is a variable
    , A, that is the cause of the confounder. Should we
    condition on it? Let's see it with the example:
\begin{lstlisting}
b_ax_i_uv_i2 <- 2
b_xy_i_uv_i2 <- 5
b_xz_i_uv_i2 <- 10
b_yz_i_uv_i2 <- 0

i_uv_i_sun.DAG <- dagitty("dag {
Sun -> UV.radiation
UV.radiation -> Ice.cream.consumption
```

```
UV.radiation -> INK4a}")

coordinates(i_uv_i_sun.DAG) <- list(x = c(Ice.cream.
    consumption = 1, UV.radiation = 2, Sun = 2, INK4a = 3)
    , y = c(Ice.cream.consumption = 3, UV.radiation = 2,
    Sun = 1, INK4a = 3))
drawdag(i_uv_i_sun.DAG)
```



As the significance of ice cream, Y, was covered in the previous function, it will be skipped in this one. We are interested in knowing if the sun, A, plays a role in the value of INK4a, Z, and how does it affect X.

```
#Necessary to create another function to create a dataset
     with other structure
create.datasetv2 <- function(b_ax, b_yz=0, N = 500, b_xy
    = 3, b_xz = 3,
                                 e_x = 1, e_y = 1, e_z = 1) {
  name_df <- data.frame(A = runif(N, 1, 100) + rnorm(N))
  name_df$X <- name_df$A * b_ax + rnorm(N, sd = e_x)
  name_df$Y <- name_df$X * b_xy + rnorm(N, sd = e_y)
  name_df$Z <- name_df$X * b_xz + name_df$Y * b_yz +
     rnorm(N, sd = e_z)
  return(name_df)}

sc1.comm.plusancestor <- function(b_yz, N, b_xz, b_xy, b_
    ax, reps = 30, e_x= 1, ...){
  onlyA_pvA <- rep(NA, reps)
  bothXA_pvA <- rep(NA,reps)
  three_pvA <- rep(NA, reps)

  onlyA_coefA <- rep(NA,reps)
  bothXA_coefA <- rep(NA, reps)
  three_coefA <- rep(NA, reps)

  onlyX_coefX <- rep(NA,reps)
```

```
bothXA_coefX <- rep(NA, reps)
three_coefX <- rep(NA, reps)

onlyX_pvX <- rep(NA, reps)
bothXA_pvX <- rep(NA, reps)
three_pvX <- rep(NA, reps)

#set.seed(13) #can be uncommented for reproducibility
for (i in 1:reps) {
  dataset <- create.datasetv2(b_yz= b_yz, N = N, b_xz =
      b_xz, b_ax = b_ax,
                                  b_xy = b_xy, e_x =e_x,
                                     ...)
  three <- lm(Z~X+A+Y, data = dataset)
  bothXA <- lm(Z~X+A, data = dataset)
  onlyA <- lm(Z~A, data = dataset)
  onlyX <- lm(Z~X, data = dataset)

  onlyA_pvA[i] <- summary(onlyA)$coefficients["A", "Pr
      (>|t|)"]
  bothXA_pvA[i] <- summary(bothXA)$coefficients["A", "
      Pr(>|t|)"]
  three_pvA[i] <- summary(three)$coefficients["A", "Pr
      (>|t|)"]

  onlyA_coefA[i] <- summary(onlyA)$coefficients["A", '
      Estimate']
  bothXA_coefA[i] <- summary(bothXA)$coefficients["A",
      "Estimate"]
  three_coefA[i] <- summary(three)$coefficients["A", "
      Estimate"]

  onlyX_coefX[i] <- summary(onlyX)$coefficients["X", '
      Estimate']
  bothXA_coefX[i] <- summary(bothXA)$coefficients["X",
      "Estimate"]
  three_coefX[i] <- summary(three)$coefficients["X", "
      Estimate"]

  onlyX_pvX[i] <- summary(onlyX)$coefficients["X", "Pr
      (>|t|)"]
  bothXA_pvX[i] <- summary(bothXA)$coefficients["X", "
      Pr(>|t|)"]
  three_pvX[i] <- summary(three)$coefficients["X", "Pr
      (>|t|)"]
  rm(dataset)}
```

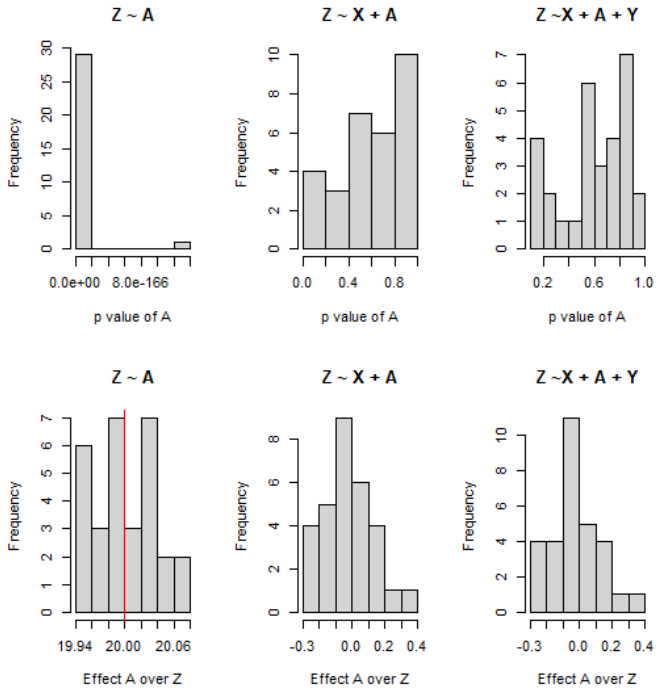
```
cat('\n____Change in p value of A on Z\n')
cat('\nWhen Z ~ A: \nThe p value of A is ', mean(onlyA_
    pvA),'\n')
cat('\nWhen Z ~ X + A: \nThe p value of A is ', mean(
    bothXA_pvA), '\n')
cat('\nWhen Z ~ Y + X + A: \nThe p value of A is ',
    mean(three_pvA), '\n')

cat('\n____Effect of A over Z\n')
cat('Input A -> X: ', b_ax,'\nInput X -> Z:', b_xz,'\
    nTotal effect A -> Z', b_xz * b_ax, '\n')
cat('\nWhen Z ~ A: \nCoefficient of A is ', mean(onlyA_
    coefA),'and its s.d. is',sd(onlyA_coefA),'\n')
cat('\nWhen Z ~ X + A: \nCoefficient of A is ', mean(
    bothXA_coefA),'and its s.d. is',sd(bothXA_coefA),'\n
    ')
cat('\nWhen Z ~ Y + X + A: \nCoefficient of A is ',
    mean(three_coefA),'and its s.d. is',sd(three_coefA),
     '\nSee plots:\n')
op <- par(mfrow= c(2,3))
hist(onlyA_pvA, main = 'Z ~ A', xlab = 'p value of A')
hist(bothXA_pvA, main = 'Z ~ X + A', xlab = 'p value of
     A')
hist(three_pvA, main='Z ~X + A + Y', xlab = 'p value of
     A')

hist(onlyA_coefA, main = 'Z ~ A', xlab = 'Effect A over
     Z')
abline(v = b_xz*b_ax, col = 'red')
hist(bothXA_coefA, main = 'Z ~ X + A', xlab = 'Effect A
     over Z')
abline(v = b_xz*b_ax, col = 'red')
hist(three_coefA, main='Z ~X + A + Y', xlab = 'Effect A
     over Z')
abline(v = b_xz*b_ax, col = 'red')
par(op)

#p value of X    ######it is very obvious that it will
    always have a significant value
#cat('\n____Change in p value of X on Z\n\nWhen Z ~ A:
    \nThe p value of X is ', mean(onlyX_pvX),'\n\nWhen Z
     ~ X +A: \nThe p value of X is ', mean(bothXA_pvX),
    '\n\nWhen Z ~ Y + X + A: \nThe p value of X is ',
    mean(three_pvX), '\n')
```

```
  cat('\n____Effect of X over Z\n\n')
  cat('Input X -> Z: ', b_xz,'\n')
  cat('\nWhen Z ~ A: \nCoefficient of X is ', mean(onlyX_
      coefX),'and its s.d. is',sd(onlyX_coefX),'\n')
  cat('\nWhen Z ~ X +A: \nCoefficient of X is ', mean(
      bothXA_coefX),'and its s.d. is', sd(bothXA_coefX),'\
      n')
  cat('\nWhen Z ~ Y + X + A: \nCoefficient of X is ',
      mean(three_coefX),'and its s.d. is', sd(three_coefX)
      ,'\nSee plots:\n')

  op <- par(mfrow= c(2,3))
  hist(onlyX_pvX, main = 'Z ~ X', xlab = 'p value of X')
  hist(bothXA_pvX, main = 'Z ~ X + A', xlab = 'p value of
       X')
  hist(three_pvX, main='Z ~X + A + Y', xlab = 'p value of
       X')

  hist(onlyX_coefX, main = 'Z ~ X', xlab = 'Effect X over
       Z')
  abline(v = b_xz, col = 'red')
  hist(bothXA_coefX, main = 'Z ~ X + A', xlab = 'Effect X
       over Z')
  abline(v = b_xz, col = 'red')
  hist(three_coefX, main='Z ~X + A + Y', xlab = 'Effect X
       over Z')
  abline(v = b_xz, col = 'red')

  par(op)}
```

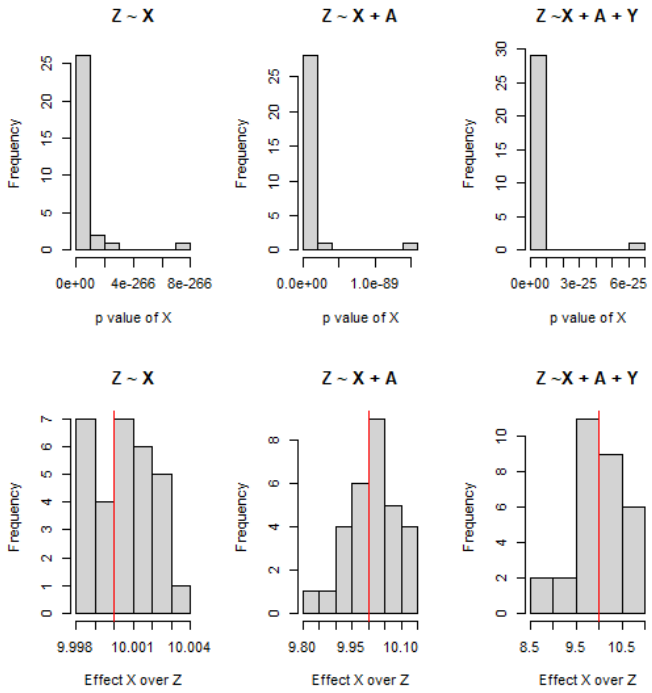
Introducing the data of the problem, the output is:

```
sc1.comm.plusancestor(b_yz = b_yz_i_uv_i2, N = samplesize
    , b_xz=b_xz_i_uv_i2, b_ax = b_ax_i_uv_i2, b_xy = b_xy_
    i_uv_i2)

#____Change in p value of A on Z
#When Z ~ A:
#The p value of A is  3.806132e-168
#When Z ~ X + A: The p value of A is  0.4372251
#When Z ~ Y + X + A:  The p value of A is  0.4176931

#____Effect of A over Z
#Input A -> X:  2
#Input X -> Z: 10
#Total effect A -> Z 20
#When Z ~ A: Coefficient of A is  20.00201 and its s.d.
```

```
    is 0.03505331
#When Z ~ X + A: Coefficient of A is  0.005650556 and its
     s.d. is 0.2130753
#When Z ~ Y + X + A: Coefficient of A is  0.005779907 and
     its s.d. is 0.2167012
#See plots:
```




```
#____Effect of X over Z
#Input X -> Z:  10
#When Z ~ X: Coefficient of X is  10.00001 and its s.d.
    is 0.002016263
#When Z ~ X + A: Coefficient of X is  10.00989 and its s.
    d. is 0.1031397
#When Z ~ Y + X + A: Coefficient of X is  10.17693 and
    its s.d. is 0.5715534 #See plots:
```

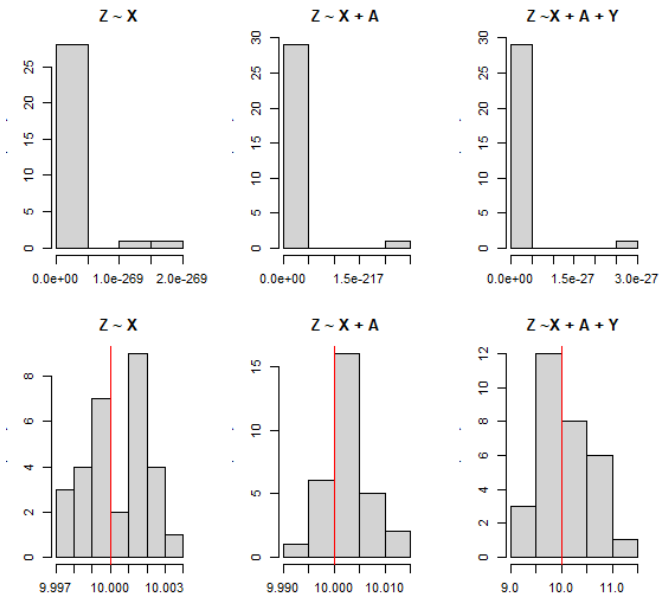


Let's first talk about A. It only has a significant p value when it is alone in the model, so the coefficients when Z X + A or Z X + A + Y are not relevant. The effect of A on Z can only be appreciated when Z A. This is supported by:

```
impliedConditionalIndependencies(i_uv_i_sun.DAG)
#INK4 _||_ Ic.. | UV.r
#INK4 _||_ Sun | UV.r
#Ic.. _||_ Sun | UV.r
```

The p value of X increases with the complexity of the model, but in any case is less significant. The estimate of X is around the expected even if complexity is increased, but its standard error gets higher. In other words, if the cause of study is UV radiation, conditioning on sun is detrimental as the variance of the coefficient increases. As seen in the cause of the cause previous work from Ramon Diaz Uriarte, when the standard error of X increases, the variance of its coefficient when Z X + A is reduced.

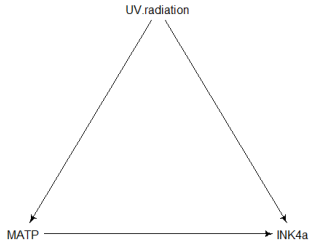
```
sc1.comm.plusancestor(b_yz = b_yz_i_uv_i2, N = samplesize
    , b_xz=b_xz_i_uv_i2, b_ax = b_ax_i_uv_i2, b_xy=b_xy_i_
    uv_i2, e_x =10)

## When Z ~ X + A: Coefficient of X is  9.999956 and its
    s.d. is 0.004412072
```


Z ~ X
Z ~ X + A
Z ~X + A + Y
0.0e+00
1.0e-269
2.0e-269
0.0e+00
1.5e-217
0.0e+00
1.5e-27
3.0e-27
Z ~ X
Z ~ X + A
Z ~X + A + Y
9.997
10.000
10.003
9.990
10.000
10.010
9.0
10.0
11.0

This function also illustrates a key property of causal inference: **same rules for simple models can be applied to more complex models**.

Let's move on to the scenario 2. We will illustrate with another example what to expect conditioning on the different possibilities. We have concluded that INK4a overexpression is caused by UV radiation. A recent study shows that there is also intervention of MATP in the French population in this process. It seems to follow the following DAG:

```
#Theoretical data
samplesize <- 100
b_xz_m_uv_i <- 4
b_yz_m_uv_i <- (-3)
b_xy_m_uv_i <- 2

m_uv_i.DAG <- dagitty("dag {
UV.radiation -> MATP
UV.radiation -> INK4a
MATP -> INK4a}")

coordinates(m_uv_i.DAG) <- list(x = c(MATP = 1, UV.
    radiation = 2, INK4a = 3),y = c(MATP = 3, UV.radiation
     = 1, INK4a = 3))
drawdag(m_uv_i.DAG)
```

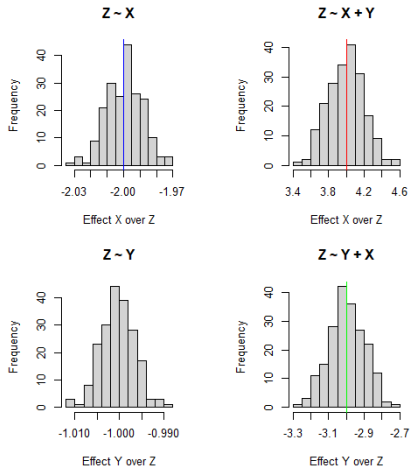


In this case, we are not just asking the question how UV radiation, X, influences INK4a, Z, but we may also be interested in how MATP, Y, affects INK4a.

```
sc2.comm <- function(b_xz, b_yz, b_xy, N, reps = 200,
    ...) {
  onlyY_pvY <- rep(NA, reps)
  both_pvY <- rep(NA, reps)
  onlyX_coefX <- rep(NA, reps)
  both_coefX <- rep(NA, reps)
  onlyY_coefY <- rep(NA, reps)
  both_coefY <- rep(NA, reps)
```

```
for (i in 1:reps){
  dataset <- create.dataset(N=N, b_xz = b_xz, b_yz = b_
      yz, b_xy = b_xy)
  both <- lm(Z~X + Y, dataset)
  onlyY <- lm(Z~Y, dataset)
  onlyX <- lm(Z~X, dataset)

  onlyY_pvY[i] <- summary(onlyY)$coefficients['Y', 'Pr
      (>|t|)']
  both_pvY[i] <- summary(both)$coefficients['Y', 'Pr(>|
      t|)']
  onlyX_coefX[i] <- summary(onlyX)$coefficients['X', '
      Estimate']
  both_coefX[i] <- summary(both)$coefficients['X', '
      Estimate']
  onlyY_coefY[i] <- summary(onlyY)$coefficients['Y', '
      Estimate']
  both_coefY[i] <- summary(both)$coefficients['Y', '
      Estimate']
  rm(dataset)}

cat('p value of Y')
cat('\nWhen Z~Y:', mean(onlyY_pvY))
cat('\nWhen Z~Y+X', mean(both_pvY),'\n\n')
cat('___Changes in X\n')
cat('When Z ~ X:\nX coefficient:', mean(onlyX_coefX), '
    s.d:', sd(onlyX_coefX))
cat('\nWhen Z ~ X + Y:\nX coefficient:', mean(both_
    coefX), 's.d:', sd(both_coefX))
cat('\n\n___Changes in Y\n')
cat('When Z ~ Y:\nY coefficient:', mean(onlyY_coefY), '
    s.d:', sd(onlyY_coefY))
cat('\nWhen Z ~ Y + X:\nY coefficient:', mean(both_
    coefY), 's.d:', sd(both_coefY))
##legend: red, direct effect X, blue total effect X,
    green effect Y
op <- par(mfrow= c(2,2))
hist(onlyX_coefX, main = 'Z ~ X', xlab = 'Effect X over
     Z')
abline(v = b_xz + b_yz*b_xy, col = 'blue')#total effect
    , it takes into account both sources of effect
abline(v = b_xz, col = 'red')#direct effect

hist(both_coefX, main = 'Z ~ X + Y', xlab = 'Effect X
    over Z')
abline(v = b_xz + b_yz*b_xy, col = 'blue')#total effect
```

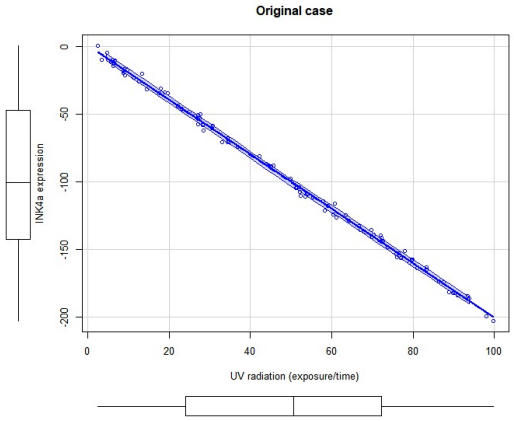
```
  abline(v = b_xz, col = 'red')#direct effect

  hist(onlyY_coefY, main = 'Z ~ Y', xlab = 'Effect X over
      Z')
  abline(v = b_yz, col = 'green')
  hist(both_coefY, main = 'Z ~ Y + X', xlab = 'Effect X
     over Z')
  abline(v = b_yz, col = 'green')
  par(op)}

sc2.comm(b_xz = b_xz_m_uv_i, b_yz = b_yz_m_uv_i, b_xy = b
    _xy_m_uv_i,
         N = samplesize)

#p value of Y
#When Z~Y: 1.157204e-134
#When Z~Y+X 7.789572e-38
#___Changes in X
#When Z ~ X: X coefficient: -2.000495 s.d: 0.01156517
#When Z ~ X + Y: X coefficient: 4.008798 s.d: 0.2082812
#___Changes in Y
#When Z ~ Y: Y coefficient: -1.00081 s.d: 0.00404317
#When Z ~ Y + X: Y coefficient: -3.004562 s.d: 0.1041344
```



In this case MATP, Y, has a significant p value in both models, in presence and absence of the common cause X, UV radiation. This makes sense and was expected. On blue it is shown the total effect of X over Z, as it takes into account the effect of X over Y as well. On red, it is shown the direct effect of X over Z. On green, the effect of Y over Z. When the mediator Y is out of the model,

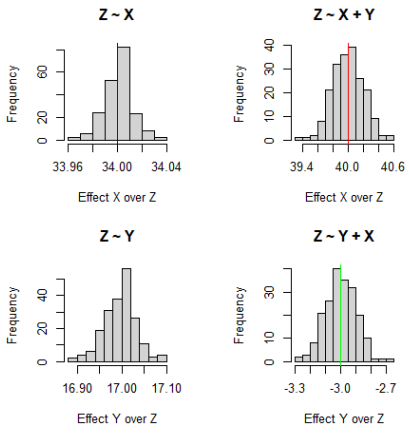
the X estimates the total effect over Z, including Y contribution. Only when Y is included it is possible to discern what is the direct effect of X. Depending on the case it would be more interesting to study the total or the direct effect of X. For this case, we argue that to know the total effect would be better because in the human body MATP expression is unavoidable. In any case, when there are two covariates in the model the variance of the estimates increase. To know the effect of Y over Z, X has to be taken into account. When UV radiation is not considered, the estimate for MATP is biased; for this reason in this kind of causal structures X is called a confounder, as in the scenario 1. To condition on Y or not may give unexpected outcomes when looking at X over Z. In this case, if MATP is not considered, it seems that the total effect is negative. If we input a higher X->Z value:

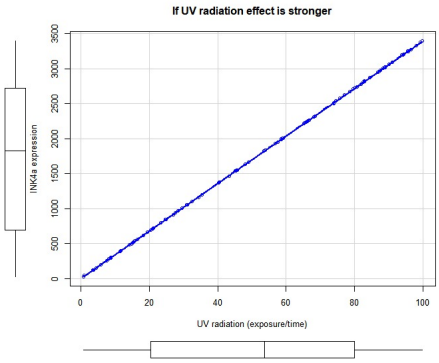
```
when_xz_4 <- create.dataset(b_xz = b_xz_m_uv_i, b_yz = b_
    yz_m_uv_i, b_xy = b_xy_m_uv_i,N = samplesize)
scatterplot(Z~X, data = when_xz_4, main ='Original case',
     regLine=TRUE)
```




```
sc2.comm(b_xz = b_xz_m_uv_i*10, b_yz = b_yz_m_uv_i, b_xy
    = b_xy_m_uv_i, N = samplesize)
when_xz_40 <- create.dataset(b_xz = b_xz_m_uv_i*10, b_yz
    = b_yz_m_uv_i, b_xy = b_xy_m_uv_i, N = samplesize)
scatterplot(Z~X, data = when_xz_40, main = 'If UV
    radiation effect is stronger', regLine=TRUE)

#p value of Y
#When Z~Y: 1.620428e-161
#When Z~Y+X 2.566037e-43
#___Changes in X
#When Z ~ X: X coefficient: 34.00068 s.d: 0.01156865
#When Z ~ X + Y: X coefficient: 39.99528 s.d: 0.2036934
```

```
#___Changes in Y
#When Z ~ Y: Y coefficient: 16.99545 s.d: 0.03612757
#When Z ~ Y + X: Y coefficient: -2.997494 s.d: 0.1018777
```

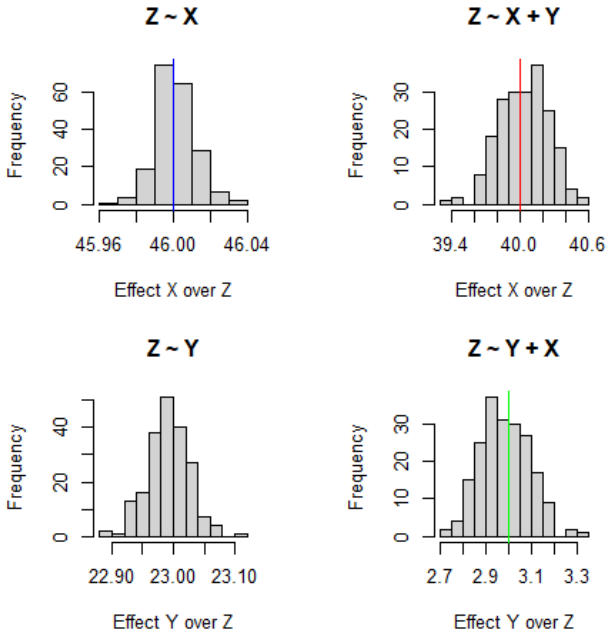




This is because the X contribution has a higher impact over Z than Y in this second case. The estimate for X in the simpler model isn't negative, it's total effect is lower than the direct effect. If the Y -> Z value wasn't negative:

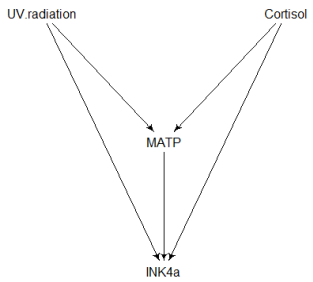
```
sc2.comm(b_xz = b_xz_m_uv_i*10, b_yz = b_yz_m_uv_i*(-1),
    b_xy = b_xy_m_uv_i, N = samplesize)
when_xz_40andnegative <- create.dataset(b_xz = b_xz_m_uv_
    i*10, b_yz = b_yz_m_uv_i*(-1), b_xy = b_xy_m_uv_i,N =
    samplesize)
scatterplot(Z~X, data = when_xz_40andnegative, main = 'If
    MATP enhances INK4a', regLine=TRUE)
#p value of Y
#When Z~Y: 2.258331e-173
#When Z~Y+X 1.924975e-41
```

```
#___Changes in X
#When Z ~ X: X coefficient: 46.00096 s.d: 0.0106993
#When Z ~ X + Y: X coefficient: 40.03247 s.d: 0.213261

#___Changes in Y
#When Z ~ Y: Y coefficient: 22.9915 s.d: 0.03411146
#When Z ~ Y + X: Y coefficient: 2.983863 s.d: 0.1064528
```



Then the effect of X, UV radiation, over Z, INK4a, is increased, as it should be obvious. The study goes on and we discovers that both the expression of MATP and INK4a is also influenced by another key factor, the cortisol level. This leaves us with the following DAG:

```
samplesize <- 100
b_by_m_uv_i_c <- 3
b_bz_m_uv_i_c <- 2
b_xz_m_uv_i_c <- 4
b_xy_m_uv_i_c <- 2
b_yz_m_uv_i_c <- (-3)

m_uv_i_c.DAG <- dagitty("dag {
UV.radiation -> MATP
UV.radiation -> INK4a
Cortisol -> MATP
Cortisol -> INK4a
MATP -> INK4a}")

coordinates(m_uv_i_c.DAG) <- list(x = c(UV.radiation = 1,
    MATP = 2, INK4a = 2, Cortisol = 3), y = c(UV.
    radiation = 1, MATP = 2, INK4a = 3, Cortisol = 1))
drawdag(m_uv_i_c.DAG)
```

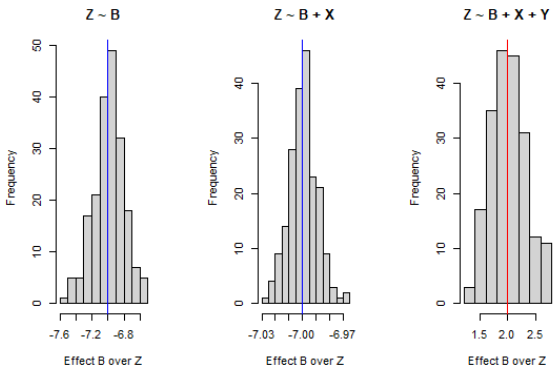


From the previous function we have learnt that the condition on the mediator variable Y, MATP, would allow us to know the direct effect of UV.radiation. When it is not present in the model, what we can see is the total effect. The reasoning behing the UV.radiation-MATP-INK4a set also apply to the Cortisol-MATP-INK4a set.

```
create.datasetv3 <- function(b_by, b_bz, b_yz=(-3), N =
    500, b_xy = 3, b_xz = 3, e_x = 1, e_y = 1, e_z = 1, e_
    b = 1) {
  name_df <- data.frame(B = runif(N, 1, 100) + rnorm(N,
      sd = e_b))
  name_df$X <- runif(N, 1, 100) + rnorm(N, sd = e_x)
```

```
  name_df$Y <- name_df$X * b_xy + name_df$B * b_by +rnorm
      (N, sd = e_y)
  name_df$Z <- name_df$X * b_xz + name_df$Y * b_yz +
    name_df$B * b_bz+ rnorm(N, sd = e_z)
  return(name_df)}

sc2.comm.extraoverY <- function(b_by, b_bz, b_xz, b_xy, b
    _yz, N, reps = 200, ...) { onlyB_coefB <- rep(NA,reps)
  bothBX_coefB <- rep(NA, reps)
  three_coefB <- rep(NA,reps)

  for (i in 1:reps){
    dataset <- create.datasetv3(N=N, b_xz = b_xz, b_yz =
        b_yz, b_xy = b_xy, b_by = b_by, b_bz = b_bz, ...)
    onlyB <- lm(Z ~ B, dataset)
    bothBX <- lm(Z ~ X + B, dataset)
    three <- lm(Z ~ Y + X + B, dataset)

    onlyB_coefB[i] <- summary(onlyB)$coefficients['B', '
        Estimate']
    bothBX_coefB[i] <- summary(bothBX)$coefficients['B',
        'Estimate']
    three_coefB[i] <- summary(three)$coefficients['B', '
        Estimate']
    rm(dataset)}

  cat('___Changes in B\n')
  cat('When Z ~ B:\nB coefficient:', mean(onlyB_coefB), '
      s.d:', sd(onlyB_coefB))
  cat('\nWhen Z ~ X + B:\nB coefficient:', mean(bothBX_
      coefB), 's.d:', sd(bothBX_coefB))
  cat('\nWhen Z ~ Y + X + B:\nB coefficient:', mean(three
      _coefB), 's.d:', sd(three_coefB))
  #legend: blue, total efffect X, red direct effect X,
      green effect Y
  op <- par(mfrow= c(1,3), mar = rep(4,4)
  hist(onlyB_coefB, main = 'Z ~ B', xlab = 'Effect B over
      Z')
  abline(v = b_bz, col = 'red')#direct effect
  abline(v = b_bz + b_yz*b_by, col = 'blue')#total effect
      of B
  hist(bothBX_coefB, main = 'Z ~ B + X', xlab = 'Effect B
      over Z')
  abline(v = b_bz, col = 'red')#direct effect
  abline(v = b_bz + b_yz*b_by, col = 'blue')#total effect
      of B
```

```
  hist(three_coefB, main = 'Z ~ B + X + Y', xlab = '
      Effect B over Z')
  abline(v = b_bz, col = 'red')#direct effect
  abline(v = b_bz + b_yz*b_by, col = 'blue')#total effect
       of B
  par(op)}

sc2.comm.extraoverY(b_by = b_by_m_uv_i_c, b_bz = b_bz_m_
    uv_i_c,
                    b_xz = b_xz_m_uv_i_c, b_xy = b_xy_m_
                        uv_i_c,
                    b_yz = b_yz_m_uv_i_c, N = samplesize
                        )
#___Changes in B
# When Z ~ B: B coefficient: -6.988085 s.d: 0.1896504
# When Z ~ X + B: B coefficient: -6.999463 s.d:
    0.01037498
# When Z ~ Y + X + B: B coefficient: 1.999542 s.d:
    0.3236159
```



The total effect of cortisol, B, is well reflected when it is on its own in the model or when UV radition, X, is considered, because they are independent from each other as can be seen in:

```
impliedConditionalIndependencies(m_uv_i_c.DAG)
# Crts _||_ UV.r
```

The variance of the coefficient when it is found along X is smaller than when B, cortisol, is checked on its own or when it also considers the collider Y, MATP. Therefore in this type of graph it would be prefered to consider both B and X on the model: the variance of the estimates is smaller and the total effect is calculated. As in the previous case, condiotioning on Y may be counterproductive. The absence of unmeasured confounding for the influence of both the exposure and the intermediate variable on the outcome is required for estimating

direct effects. If both of these requirements are not satisfied, no approach can offer unbiased estimates of exposure's direct effects. This last causal structure introduce us to the next issue: colliders and common effect cases.

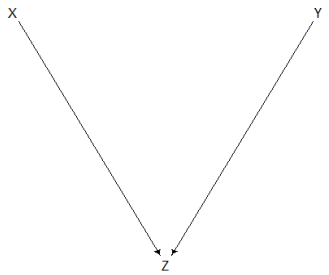
3 What to do when there is a common effect

In this second section, we are going to analyze the problems and biases you can create by not controlling a particular case of covariates: the colliders. When studying the effects of differents variables on a particular one, and the difficulties of adjusting by the collider, Z, when X and Y are its parents and may or may not have an association between them. In this case Z is the **common effect** of X and Y. We have used the following modules to make the analysis:

```
library(dagitty)
if(!suppressWarnings(require("rethinking",
quietly = TRUE))) {drawdag <- plot}
```

The variable X can have an effect on Y or not. This gives us two basic scenarios to work on.The first scenario is illustrated in the following DAG:

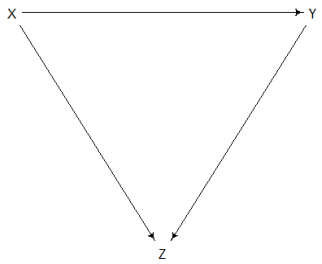
```
comm.effect.DAG <- dagitty("dag {
X -> Z
Y -> Z
}")

coordinates(comm.effect.DAG) <- list(x = c(X = 1, Y = 3,
    Z = 2),
                                     y = c(X = 1, Y = 1,
                                         Z = 3))
drawdag(comm.effect.DAG)
```



For this first case, X is not associated to Y. The second scenario would be:

```
DAG_Situation2 <- dagitty("dag {
X -> Z
Y -> Z
X -> Y
```

```
}")

coordinates(DAG_Situation2) <- list(x = c(X = 1, Y = 3, Z
    = 2),
                                    y = c(X = 1, Y =
                                        1, Z = 3))
drawdag(DAG_Situation2)
```



In this second case, X does have an effect over Y. Whether this two variables do or do not affect each other is important in terms of what kind of effect the adjustment of the collider will have on each one. For the first case, adjusting on the collider will create an association not present before. For the second one, the association between the variables already existed, so what happens is that when we adjust for our collider the direction of that relation might change. For this part, we will simulate our data using vectors. Let's see how we are going to do that for case 1 and case 2.

Let us begin with case 1:

```
N <- 500 # Our sample size throughout the whole code will
    be 500
b_xz <- 3 # The value of the relation between X and Z is
    3
b_yz <- 2 # The value of the relation between Y and Z is
    2
sd_z <- 1 # The standard deviation for Z will be 5

# We will try not to repeat this information description
    as we already know what
# each variable represents.

X <- runif(N, 1, 10)
Y <- runif(N, 1.5, 12)
Z <- b_xz * X + b_yz * Y + rnorm(N, 0, sd = sd_z)
```

We use vectors to generate random numbers from 1 to 10 for our X variable and from 1.5 to 12 for our Y variable, as both are independent. For our collider Z we multiply the values of the two previous variables by a number we want to set as the relation between the parents $XandY$ and the collider Z. We also add our standard deviation.

Now for our case number 2:

```
b_xy2 <- 1.7
b_xz2 <- 1.5
b_yz2 <- 2.5

X2 <- runif(N, 1, 10)
Y2 <- X2 * b_xy2 + rnorm(N, mean = 0, sd = 1)
Z2 <- X2 * b_xz2 + Y2 * b_yz2 + rnorm(N, mean = 0, sd =
    1)
```

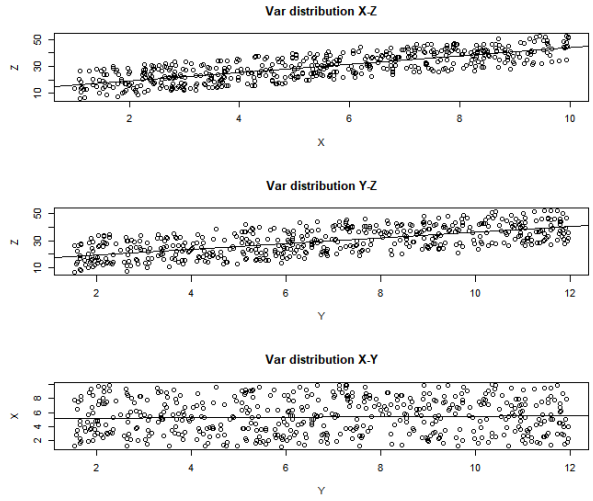
In this case there **is** a relation between X2 and Y2, so for that, we generate the values for Y2 by multiplying our b̈_xy2änd our X values. We do the same process for the Z2 values as we did for Z in our previous case.

Next we will see a function created to generate plots for the regression between two variables, adding our abline. This function will come in handy when we want to check the distribution of our data.

```
PLOT.REG <- function(reg_line, plot.var = '') {
  Regres.line <- lm(reg_line)
  plot(reg_line, main = plot.var)
  abline(Regres.line)
}
```

The function is quite simple, there is a manual for this particular function and it can be checked in the repository in case more information is needed.

```
op <- par(mfrow= c(3, 1))
PLOT.REG(Z ~ X, 'Var distribution X-Z')
PLOT.REG(Z ~ Y, 'Var distribution Y-Z')
PLOT.REG(X ~ Y, 'Var distribution X-Y')
par(op)
```



As we can see, there is, apparently, a positive correlation between Z and X and also Z and Y. On the other hand, there is no visible correlation between X and Y *asshould*. We can check it by calculating the estimates and significance of each pair. For that we will create a function that accepts the following arguments: variables to check, dependent variable *togettheestimateandpvalue*, and the title of the variables; the last two ones should be text input in order to make it work.

Now that we already checked the distribution of our data, now we should check for our estimates and p values to see if that association or lack thereof is also visible in our values. To do so, we created a function that returns a string that reveals whether there is an association or not, and the values for the estimate and pvalue for our two variables.

```
SUM.2VAR <- function(variable1, v_dep1, title_var1,
    variable2,
                         v_dep2, title_var2, ...){
  PV1 <- summary(lm(variable1))$coefficients[v_dep1, 'Pr
      (>|t|)']
  E1 <- summary(lm(variable1))$coefficients[v_dep1, '
      Estimate']

  PV2 <- summary(lm(variable2))$coefficients[v_dep2, 'Pr
      (>|t|)']
  E2 <- summary(lm(variable2))$coefficients[v_dep2, '
      Estimate']

  P.VAL.DICT <- new.env(hash = T, parent = emptyenv())
```

```
  assign(title_var1, PV1, P.VAL.DICT)
  assign(title_var2, PV2, P.VAL.DICT)

  E.DICT <- new.env(hash = T, parent = emptyenv())
  assign(title_var1, E1, E.DICT)
  assign(title_var2, E2, E.DICT)

  for (i in ls(P.VAL.DICT)) {
    if (P.VAL.DICT[[i]] > 0.05)
      cat('The variables', i, 'do not show an association
          with a p value of',
          P.VAL.DICT[[i]], 'and an estimate of', E.DICT[[
              i]], '\n')
    else
      cat('The variables', i, 'show an association with a
          p value of',
          P.VAL.DICT[[i]], 'and an estimate of', E.DICT[[
              i]], '\n')}
} # SUMMARY for 2 variables

SUM.3VAR <- function(variable1, v_dep1, title_var1,
    variable2,
                     v_dep2, title_var2, variable3, v_
                         dep3, title_var3){
  PV1 <- summary(lm(variable1))$coefficients[v_dep1, 'Pr
      (>|t|)']
  E1 <- summary(lm(variable1))$coefficients[v_dep1, '
      Estimate']

  PV2 <- summary(lm(variable2))$coefficients[v_dep2, 'Pr
      (>|t|)']
  E2 <- summary(lm(variable2))$coefficients[v_dep2, '
      Estimate']

  PV3 <- summary(lm(variable3))$coefficients[v_dep3, 'Pr
      (>|t|)']
  E3 <- summary(lm(variable3))$coefficients[v_dep3, '
      Estimate']

  P.VAL.DICT <- new.env(hash = T, parent = emptyenv())
  assign(title_var1, PV1, P.VAL.DICT)
  assign(title_var2, PV2, P.VAL.DICT)
  assign(title_var3, PV3, P.VAL.DICT)

  E.DICT <- new.env(hash = T, parent = emptyenv())
  assign(title_var1, E1, E.DICT)
```

```
  assign(title_var2, E2, E.DICT)
  assign(title_var3, E3, E.DICT)

  for (i in ls(P.VAL.DICT)) {
    if (P.VAL.DICT[[i]] > 0.05)
      cat('The variables', i, 'do not show an association
          with a p value of',
          P.VAL.DICT[[i]], 'and an estimate of', E.DICT[[
              i]], '\n')
    else
      cat('The variables', i, 'show an association with a
          p value of',
          P.VAL.DICT[[i]], 'and an estimate of', E.DICT[[
              i]], '\n')}
} # SUMMARY for 3 variables

SUM.4VAR <- function(variable1, v_dep1, title_var1,
    variable2,
                     v_dep2, title_var2, variable3, v_
                         dep3, title_var3,
                     variable4, v_dep4, title_var4){
  PV1 <- summary(lm(variable1))$coefficients[v_dep1, 'Pr
      (>|t|)']
  E1 <- summary(lm(variable1))$coefficients[v_dep1, '
      Estimate']

  PV2 <- summary(lm(variable2))$coefficients[v_dep2, 'Pr
      (>|t|)']
  E2 <- summary(lm(variable2))$coefficients[v_dep2, '
      Estimate']

  PV3 <- summary(lm(variable3))$coefficients[v_dep3, 'Pr
      (>|t|)']
  E3 <- summary(lm(variable3))$coefficients[v_dep3, '
      Estimate']

  PV4 <- summary(lm(variable4))$coefficients[v_dep4, 'Pr
      (>|t|)']
  E4 <- summary(lm(variable4))$coefficients[v_dep4, '
      Estimate']

  P.VAL.DICT <- new.env(hash = T, parent = emptyenv())
  assign(title_var1, PV1, P.VAL.DICT)
  assign(title_var2, PV2, P.VAL.DICT)
  assign(title_var3, PV3, P.VAL.DICT)
  assign(title_var4, PV4, P.VAL.DICT)
```

```
  E.DICT <- new.env(hash = T, parent = emptyenv())
  assign(title_var1, E1, E.DICT)
  assign(title_var2, E2, E.DICT)
  assign(title_var3, E3, E.DICT)
  assign(title_var4, E4, E.DICT)

  for (i in ls(P.VAL.DICT)) {
    if (P.VAL.DICT[[i]] > 0.05)
      cat('The variables', i, 'do not show an association
          with a p value of',
          P.VAL.DICT[[i]], 'and an estimate of', E.DICT[[
              i]], '\n')
    else
      cat('The variables', i, 'show an association with a
          p value of',
          P.VAL.DICT[[i]], 'and an estimate of', E.DICT[[
              i]], '\n')}
} #SUMMARY for 4 variables


#Let's check our variables:
SUM.4VAR(X ~ Z, "Z", "X and Z", Y ~ Z, "Z", "Y and Z", X
    ~ Y, "Y", "X and Y", X ~ Y + Z,
         "Y", "X and Y (when Z)")

#The variables X and Y do not show an association with a
    p value of 0.3328062 and an #estimate of 0.03488318
#The variables X and Y (when Z) show an association with
    a p value of 0 and an estimate of
#-0.6506454
#The variables X and Z show an association with a p value
     of 6.677158e-103 and an estimate #of 0.1942392
#The variables Y and Z show an association with a p value
     of 5.433219e-62 and an estimate of #0.2025114
```

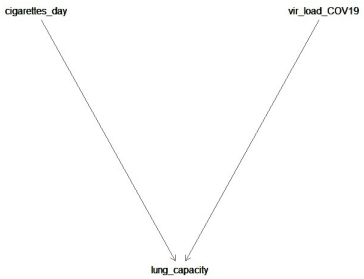
We can see a strong correlation between Z and X. There is also a positive relation between Z and Y, but none between X and Y. But the two independent variables $XandY$ when we adjust by Z raise a correlation that wasn't supposed to be there. When controling a collider, you can induce a bias in the estimate of theparent variables when there is, actually, none. Knowing now well how to check our estimates and pvalues to aknowledge the association between the two variables $XandY, whateverthosemightbe$, let's explore a more realistic example:

Here we have a set of variables: cigarettes smoked in a day, COVID19 virus load and % of lung capacity. Both cigarette consumption and virus load should

affect the lung capacity, but there should not be a relation between the number of cigarettes consumed daily and the COV19 virus load.

Let's take a look at the DAG:

```
DAG.Lung <- dagitty("dag {
cigarettes_day -> lung_capacity
vir_load_COV19 -> lung_capacity
}")

coordinates(DAG.Lung) <- list(x = c(cigarettes_day = 1,
    vir_load_COV19 = 3,
                                        lung_capacity = 2),
                                  y = c(cigarettes_day = 1,
                                      vir_load_COV19 = 1,
                                          lung_capacity = 3))
drawdag(DAG.Lung)
```

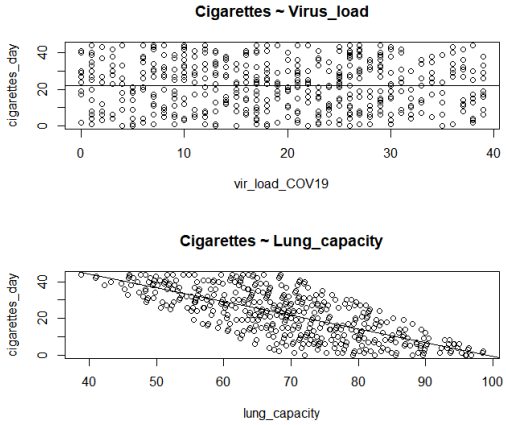


We now simulate the data for this particular example, in which both cigarettes and virus load are numerical values, while lung capacity is expressed as a percentage.

```
b_cd <- (-0.7) # Relation between cigarettes and lung
    capacity
b_vlc <- (-0.8) # Relation between virus load and lung
    capacity

cigarettes_day <- floor(runif(N, min = 0, max = 45)) #
    number of cig a day
vir_load_COV19 <- floor(runif(N, min = 0, max = 40)) #Ct
lung_capacity <- 100 + b_cd * cigarettes_day + b_vlc *
    vir_load_COV19 +
  rnorm(N, 0, sd = 0.01) #percentage of lung capacity
```

Here we have the plots showing the distribution of the variables cigarettes_day and vir_load_COV19, where apparently there is no correlation.

```
op <- par(mfrow= c(2, 1))
PLOT.REG(cigarettes_day ~ vir_load_COV19, "Cigarettes ~
    Virus_load")

# A plot for comparison, cigarettes and lung capacity, a
    negative correlation:
PLOT.REG(cigarettes_day ~ lung_capacity, "Cigarettes ~
    Lung_capacity")

par(op)
```



Let's see the relations between our variables.

```
SUM.4VAR(cigarettes_day ~ lung_capacity, "lung_capacity",
     "cigarettes and lung capacity",
          vir_load_COV19 ~ lung_capacity, "lung_capacity",
               "vir_load_COV19 and lung capacity",
          cigarettes_day ~ vir_load_COV19, "vir_load_COV19
              ", "cigarettes and vir_load_COV19",
           cigarettes_day ~ vir_load_COV19 + lung_capacity
               , "vir_load_COV19",
          "cigarettes and vir_load_COV19 (when lung
              capacity)")


#The variables cigarettes and lung capacity show an
    association with a p value of 3.086284e-83 and an
    estimate of -0.756362
```

```
#The variables cigarettes and vir_load_COV19 do not show
    an association with a p value of 0.9486949 and an
    estimate of -0.003496631
#The variables cigarettes and vir_load_COV19 (when lung
    capacity) show an association with a p value of 0 and
    an estimate of -1.142745
#The variables vir_load_COV19 and lung capacity show an
    association with a p value of 1.787942e-70 and an
    estimate of -0.5881356
```

No correlation between number of cigarettes smoked a day and the viral load of COV19 infection but a correlation between these two variables arises when adjusting for the collider *lung_capacity*.

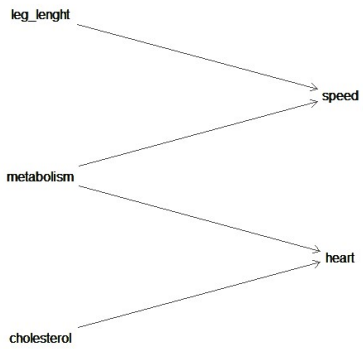
At this point we have already seen how adjusting a collider may create some problems when analyzing data. But things can get a lot more complicated. Let's not go too far, but see a new example which is a bit more complicated than the previous ones.

Imagine we are studying the performance of a professional runner. We have a few variables to take into consideration, but we will focus on the following ones: leg length,metabolism (which affects weight, meaning it also affects performance), heart disease (measured through the values of high-sensitivity cardiac troponin (hs-cTn)), cholesterol (as a measure of overall health); this last variable does not affect directly the performance of the runner (speed), but it might through its health.

Let's take a look at the DAG:

```
DAG.Runner <- dagitty("dag {
cholesterol -> heart
metabolism -> heart
metabolism -> speed
leg_lenght -> speed
}")

coordinates(DAG.Runner) <- list(x = c(cholesterol = 1,
    heart = 3,
                                      metabolism
                                          = 1,
                                          speed =
                                          3,
                                      leg_lenght
                                          = 1),
                                y = c(cholesterol
                                    = 5, heart = 4,
                                        metabolism =
                                          3, speed
                                          = 2,
```

```
                                                    leg_lenght =
                                                        1))
drawdag(DAG.Runner)
```



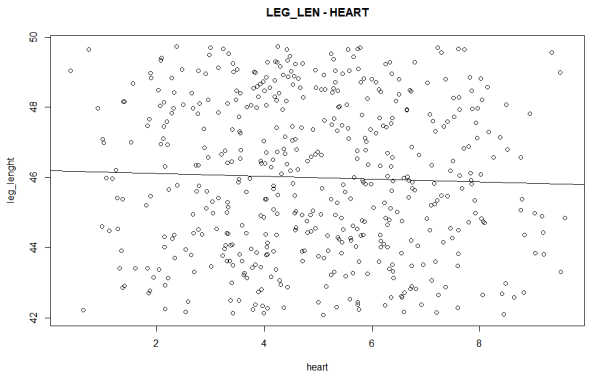
Let's, one more time, generate the data. In this case we have 5 variables, some are associated, others not, it's all on the next piece of code:

```
b_ll_s <- 1.2
b_m_s <- 1
b_ch_h <- 0.05
b_m_h <- (-0.3)

leg_lenght <- runif(N, max = 49.75, min = 42.09) #cm
metabolism <- runif(N, 1, 20) # Theoretically this
    variable is unmeasured
cholesterol <- runif(N, 125, 200) #mg/dL
speed <- leg_lenght * b_ll_s + metabolism * b_m_s + rnorm
    (N, mean = 0,
                                                    sd
                                                      =
                                                      5)
                                                      #
                                                      mph

heart <- cholesterol * b_ch_h + metabolism * b_m_h +
    rnorm(N, mean = 0,
                                                    sd
```

```
=

0.1)

#
ng
/
L
```

Again, let's take a look at the plots for the distribution:

```
PLOT.REG(leg_lenght ~ heart, "LEG_LEN ~ HEART")
```



Let's, one more time, check the relations:

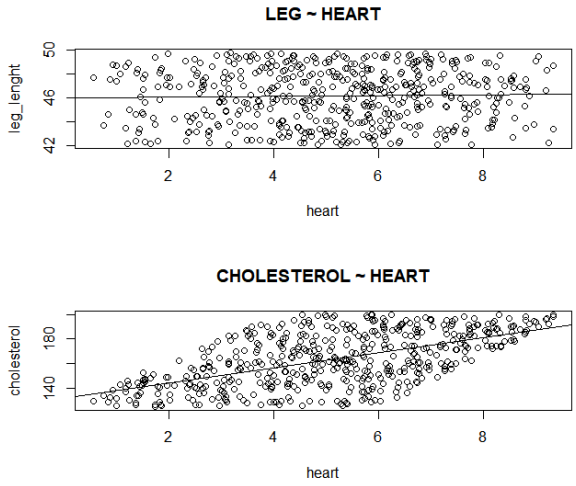
```
SUM.4VAR(leg_lenght ~ metabolism, "metabolism", "leg_len
    and metabolism", leg_lenght ~ cholesterol,
        "cholesterol", "leg_len and cholesterol", leg_
            lenght ~ heart, "heart", "leg_len and heart",
        leg_lenght ~ heart + speed, "heart", "leg_len
            and heart (when speed)")


#The variables leg_len and cholesterol do not show an
    association with a p value of 0.841257 and an estimate
     of -0.0009198866
#The variables leg_len and heart do not show an
    association with a p value of 0.5383972 and an
    estimate of 0.0302165
#The variables leg_len and heart (when speed) show an
    association with a p value of 3.277156e-12 and an
```

```
    estimate of 0.3962244
#The variables leg_len and metabolism do not show an
    association with a p value of 0.3730765 and an
    estimate of -0.01604611
```

There is no correlation between leg lenght and metabolism, leg lenght and cholesterol and leg lenght and heart disease; but when we adjust for the collider speed, we open a path between leg lenght and heart disease. We do find a correlation between heart when there is no correlation between how long your legs are and cardiac disease.

Let's look at our data one more time and see whether this correlation we find when adjusting by our collider (speed) is actually present. The second plot shows the correlation that actually exists between the variables cholesterol and heart, as opposed to the previous ones (for comparison).

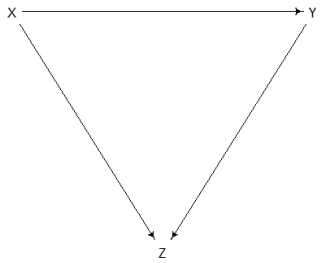
```
op <- par(mfrow= c(2, 1))
PLOT.REG(leg_lenght ~ heart, "LEG ~ HEART")

PLOT.REG(cholesterol ~ heart, "CHOLESTEROL ~ HEART")

par(op)
```



Let's dive in into our second case. In this situation our X and Y variables have some sort of relation but the estimate (its correlation) changes from positive to negative when we condition on Z (collider).

Let's take another peak at the DAG to remind us of the structure:

We, again, generate random data, but in this case the values of Y are associated to the ones from X:




```
b_xy2 <- 1.7
b_xz2 <- 1.5
b_yz2 <- 2.5

X2 <- runif(N, 1, 10)
Y2 <- X2 * b_xz2 + rnorm(N, mean = 0, sd = 1)
Z2 <- X2 * b_xz2 + Y2 * b_yz2 + rnorm(N, mean = 0, sd =
    1)
```

Let's check our data:

```
op <- par(mfrow= c(3, 1))

PLOT.REG(Z2 ~ X2, "Var distribution Z2 ~ X2")
PLOT.REG(Z2 ~ Y2, "Var distribution Z2 ~ Y2")
PLOT.REG(X2 ~ Y2, "Var distribution X2 ~ Y2")

par(op)
```

As we can see, there is, apparently a positive correlation between Z2 and X2; Z2 and Y2; and X2 and Y2. In this case we are interested in the relationship between X2 and Y2; we can check it:

```
SUM.2VAR(X2 ~ Y2, "Y2", "X2 and Y2", X2 ~ Y2 + Z2, "Y2",
    "X2 and Y2 (when Z2)")


#The variables X2 and Y2 show an association with a p
    value of 1.074789e-301 and an estimate of 0.6174945
#The variables X2 and Y2 (when Z2) show an association
    with a p value of 2.690063e-19 and an estimate of
    -0.4720634
```

The positive correlation we find between X2 and Y2 switches to a negative correlation when we adjust for Z2. As we can see, in this particular case, conditioning on Z changes the sign of the estimate for the Y2 variable, as in Simpson's paradox

Now, with a more practical example:

We want to study the effect of UV radiation (hours of exposure a day) and INK4a on the mutation of gen p53. First of all we illustrate the causal structure:

```
DAG.p53 <- dagitty("dag {
UV_radiation -> mutated_p53
INK4a -> mutated_p53
UV_radiation -> INK4a
}")

coordinates(DAG.p53) <- list(x = c(UV_radiation = 1,
    INK4a = 3,
                                   mutated_p53 = 2),
                             y = c(UV_radiation = 1, INK4a
                                 = 1,
                                   mutated_p53 = 3))
drawdag(DAG.p53)
```

Let's generate our data for this particular case:

```
b_UV_INK4a <- 0.2
b_INK4a_mp53 <- 2
b_UV_mp53 <- 0.7


UV_radiation <- runif(N, 0, 9)
INK4a <- UV_radiation * b_UV_INK4a + rnorm(N, mean = 0,
    sd = 0.5)
mutatedp53 <- UV_radiation * b_UV_mp53 + INK4a * b_INK4a_
    mp53 +
  rnorm(N, mean = 0, sd = 0.1)
```

Again lets gather our data in a dataframe to check it:

```
PLOT.REG(UV_radiation ~ INK4a, 'UV ~ INK4a')


SUM.2VAR(UV_radiation ~ INK4a, "INK4a", "UV and INK4a",
    UV_radiation ~ INK4a
          + mutatedp53, "INK4a", "UV and INK4a (when Mp53)
              ")
```

```
#The variables UV and INK4a show an association with a p
    value of 4.878714e-87 and an estimate of 2.647573
#The variables UV and INK4a (when Mp53) show an
    association with a p value of 0 and an estimate of
    -2.81791
```

As shown in the Summary function, the correlation between the variables UV radiation is maintained after adjusting for the collider but the relation that was once positive becomes negative when adjusting for Mp53 (collider)

Now that we have seen how adjusting the collider can afect the estimates and pvalues, we should also check two more scenarios: Ancestors and Descendants.Let's start with the ancestors:

Imagine we have now a variable Z (a collider) that has an ancestor *variableW*, does conditioning on any of those two affect the relation between variable X and Y?

Let's draw our DAG:

```
DAG_Ancestor <- dagitty("dag {
X -> Z
Y -> Z
W -> Z
}")

coordinates(DAG_Ancestor) <- list(x = c(X = 1, Y = 3, Z =
    2, W = 2),
                                  y = c(X = 1, Y =
                                      1, Z = 2, W =
                                      3))
drawdag(DAG_Ancestor)
```

As always, we create the data according to our DAG:

```
b_xz <- 3
b_yz <- 2
b_wz <- 2.5
sd_z <- 1


X3 <- runif(N, 1, 5)
Y3 <- runif(N, 2, 4)
W3 <- runif(N, 1.5, 3)
Z3 <- b_xz * X3 + b_yz * Y3 + W3 * b_wz + rnorm(N, 0, sd
    = sd_z)
```

And once again we will be checking the summaries for our estimates and pvalues, but this time we want to check also what happens when we adjust for the ancestor of our collider W.

```
SUM.4VAR(X3 ~ W3, "W3", "X3 and W3", X3 ~ W3 + Z3, "W3",
    "X3 and W3 (when Z3)", X3 ~ Y3 + Z3,
          "Y3", "X3 and Y3 (when Z3)", X3 ~ Y3, "Y3", "X3
              and Y3")


#The variables X3 and W3 show an association with a p
    value of 0.02225708 and an estimate of 0.2704141
#The variables X3 and W3 (when Z3) show an association
    with a p value of 6.253145e-32 and an estimate of
    -0.6510684
#The variables X3 and Y3 do not show an association with
    a p value of 0.7848218 and an estimate of -0.02393977
#The variables X3 and Y3 (when Z3) show an association
    with a p value of 1.57704e-41 and an estimate of
    -0.5242863
```

There is no significant correlation between X3 and W3, but when conditioned for Z3 a negative correlation arises. Same thing hapopens between the variables X3 and Y3. Therefore, conditioning on Z3 modifies the independence between X3, Y3 and W3

```
SUM.2VAR(X3 ~ Y3, "Y3", "X3 and Y3", X3 ~ Y3 + W3, "Y3",
    "X3 and Y3 (when W3)")


#The variables X3 and Y3 do not show an association with
    a p value of 0.7848218 and an estimate of -0.02393977
#The variables X3 and Y3 (when W3) do not show an
    association with a p value of 0.8489813 and an
    estimate of -0.01663633
```

No significant correlation found between X3 and Y3, nor can we find a correlation when adjusting for the ancestor (W3). So, conditioning on W3 does not change the independence between X3 and Y3.

Let's take a look at a more realistic example: we want to study the effect of cortisol and cholesterol on diabetes, but we also have to take into consideration the variable "sugar consumption in gr". Here is the DAG:

```
DAG.Diabetes.Ancestor <- dagitty("dag {
cortisol -> diabetes
```

```
cholesterol -> diabetes
sugar_consumpt -> diabetes
}")

coordinates(DAG.Diabetes.Ancestor) <- list(x = c(cortisol
    = 1, cholesterol = 3,
                                                diabetes = 2,
                                                 sugar_
                                                    consumpt =
                                                     2),
                                            y = c(cortisol =
                                                1, cholesterol
                                                = 1,
                                                   diabetes =
                                                     2,
                                                   sugar_
                                                     consumpt
                                                     = 3))
drawdag(DAG.Diabetes.Ancestor)


b_co_d <- 0.9
b_ch_d <- 0.95
b_sc_d <- 1.2
sd_d <- 1


cortisol <- runif(N, 1, 50)
cholesterol <- runif(N, 10, 250)
diabetes <- cortisol * b_co_d + cholesterol * b_ch_d +
    sug_consumption *
  b_sc_d+ rnorm(N, 0, sd = sd_d)
sug_consumption <- runif(N, 0, 150)


PLOT.REG(cortisol ~ cholesterol, 'cortisol ~ cholesterol'
    )


SUM.2VAR(cortisol ~ cholesterol, "cholesterol", "cortisol
    and cholesterol", cortisol
         ~ cholesterol + sug_consumption, "cholesterol",
           "colesterol and cortisol (when sugar)")
```

```
#The variables colesterol and cortisol (when sugar) do
    not show an association with a p value of 0.4571814
    and an estimate of 0.006613713
#The variables cortisol and cholesterol do not show an
    association with a p value of 0.4510984 and an
    estimate of 0.006693875
```

Again we find no correlation between cortisol and cholesterol, even if we adjust for the ancestor (sugar_consumption).

```
SUM.2VAR(cortisol ~ cholesterol, "cholesterol", "cortisol
    and cholesterol", cortisol
        ~ cholesterol + diabetes, "cholesterol", "
          colesterol and cortisol (when diabetes)")

#The variables colesterol and cortisol (when diabetes)
    show an association with a p value of 7.764322e-07 and
     an estimate of -0.07041942
#The variables cortisol and cholesterol do not show an
    association with a p value of 0.4510984 and an
    estimate of 0.006693875
```

But we do find a correlation between those two variables when adjusting for diabetes *thecollider*.

Let's take a look at our second possible scenario with the ancestor and descendant situations. We now have a variable Z *acollider* that has a descendant *variableW*, does conditioning on any of those two affect the relation between variable X and Y? Starting with the DAG:

```
DAG.Descendant <- dagitty("dag {
X -> Z
Y -> Z
Z -> W
e_z -> Z
}")

coordinates(DAG.Descendant) <- list(x = c(X = 1, Y = 3, Z
    = 2,
                                          e_z = 1.75,
                                            W = 2),
                                    y = c(X = 1, Y =
                                        1, Z = 2,
                                          e_z = 2, W =
                                            3))
drawdag(DAG.Descendant)
```

We generate the data...

```
b_xz <- 1.1
b_yz <- 0.7
b_zw <- 2
sd_z <- 0.5
sd_w <- 0.5

X4 <- runif(N, 1, 10)
Y4 <- runif(N, 2, 20)
Z4 <- b_xz * X4 + b_yz * Y4 +  rnorm(N, 0, sd = sd_z)
W4 <- b_zw * Z4 + rnorm(N, 0, sd = sd_w)
```

And check our estimates and pvalues once more:

```
SUM.3VAR(X4 ~ Y4, "Y4", "X4 and Y4", X4 ~ Y4 + W4, "Y4",
    "X4 and Y4 (when W4)", X4 ~ Y4 + Z4,
          "Y4", "X4 and Y4 (when Z4)")

#The variables X4 and Y4 do not show an association with
    a p value of 0.471942 and an estimate of -0.01698028
#The variables X4 and Y4 (when W4) show an association
    with a p value of 8.300303e-322 and an estimate of
    -0.6199551
#The variables X4 and Y4 (when Z4) show an association
    with a p value of 0 and an estimate of -0.6217867
```

We find no correlation between X4 and Y4, but when we condition on the collider Z or its descendant $W4$ we find a significantly negative correlation between the two variables. In this case adjusting by Z4 and W4 *itsdescendant* resulted in a correlation between the variables X4 and Y4.

Practical example: we want to see how does diabetes affect heart disease for that we will also measure cortisol and cholesterol, which affect diabetes. Let's see what happens when we condition the collider or its descendant in this particular case. First we create the DAG:

```
DAG.Diabetes.Descendant <- dagitty("dag {
cortisol -> diabetes
cholesterol -> diabetes
diabetes -> heart_disease
}")

coordinates(DAG.Diabetes.Descendant) <- list(x = c(
    cortisol = 1,
                                              cholesterol = 3,
                                                 diabetes = 2,
```

```
                                                heart_disease =
                                                    2),
                                            y = c(cortisol =
                                                1, cholesterol
                                                = 1,
                                                    diabetes =
                                                        2,
                                                    heart_
                                                        disease =
                                                         3))
drawdag(DAG.Diabetes.Descendant)
```

As the example is very simmilar to the previous one, we well be using the same values for the data, excepting the heart disease variable.

```
b_co_d_d <- 1.5
b_ch_d_d <- 0.95
b_d_hd <- 2.5
sd_d_d <- 5
sd_hd <- 2
```

```
cortisol_desc <- runif(N, 1, 50)
cholesterol_desc <- runif(N, 10, 250)
diabetes_desc <- cortisol_desc * b_co_d_d + cholesterol_
    desc * b_ch_d_d +
  rnorm(N, 0, sd = sd_d_d)
heart_disease <- diabetes_desc * b_d_hd + rnorm(N, 0, sd
    = sd_hd)
```

Let's check the values...

```
SUM.3VAR(cortisol_desc ~ cholesterol_desc, "cholesterol_
    desc", "cortisol and cholesterol",
          cortisol_desc ~ cholesterol_desc + diabetes_desc
              , "cholesterol_desc",
          "cortisol and cholesterol (when diabetes)",
              cortisol_desc ~ cholesterol_desc + heart_
              disease,
          "cholesterol_desc", "cortisol and cholesterol (
              when heart disease)")
```

```
#The variables cortisol and cholesterol do not show an
    association with a p value of 0.424835 and an estimate
     of -0.007447195
```

```
#The variables cortisol and cholesterol (when diabetes)
    show an association with a p value of 8.388719e-309
    and an estimate of -0.6025828
#The variables cortisol and cholesterol (when heart
    disease) show an association with a p value of
    1.393365e-304 and an estimate of -0.6017466
```

Just like in our previous simple example, in this case there should not be any relation between cortisol and cholesterol (as we did intend with our data) and when we see our summary we can confirm there is no relation. But when we condition on our collider or its descendant (heart disease) a correlation between the variables cortisol and cholesterol arises.

To better visualize this non existent correlation between our two variables we can check the plot for the regression of both of them and it's pretty clear that there is no apparent positive or negative correlation. To reinforce this data, we can also check and compare the plot for the variables cortisol and heart disease, where we see a positive correlation.

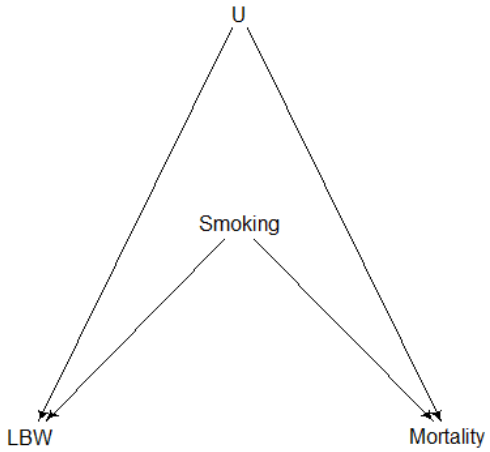
```
op <- par(mfrow= c(2, 1))

PLOT.REG(cortisol_desc ~ cholesterol_desc, 'cortisol ~
    cholesterol')

PLOT.REG(cortisol_desc ~ heart_disease, 'cortisol ~ heart
    _disease')
```

4 Complex cases and backdoor criteria

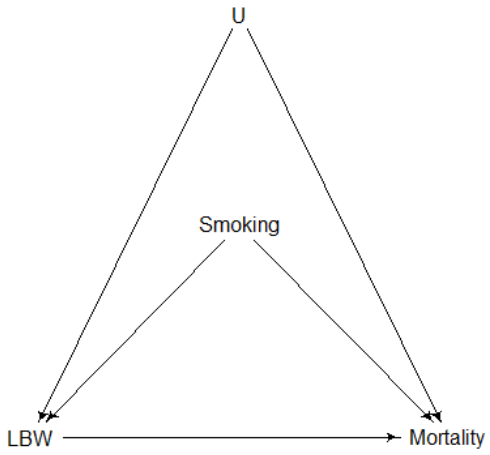
To develop this issue, we will need the following packages:

```
library(simstudy)
library(dagitty)
library(rethinking)
if(!suppressWarnings(require("rethinking", quietly = TRUE
    ))) {drawdag <- plot}
\end{lstlistings}

A complex causal phenomenom that has been studied for
    long is the Simpson's paradox: there is a trend
    between variables when different groups of data are
    observed, but when the groups are combined, this trend
     disappears or is reversed. This paradox is commonly
    explained as a extreme case of confounding, though
    some experts argue that this is a oversimplification
    \(Hernan, 2017\).
```

```
One striking example of Simpson's paradox is the low
    birth-weight paradox. It will also help us to
    introduce the problem that may involve the unmeasured
    variables: those events that may affect the causal
    structure of our model but can't be measured, or that
    we are not even aware of. This example presents the
    same issue in any of the following two directed
    acyclic graphs:
\begin{lstlisting}
LBWsc1.DAG <- dagitty('dag {
Smoking -> LBW
Smoking -> Mortality
U -> LBW
U -> Mortality}')

coordinates(LBWsc1.DAG) <- list(x = c(LBW = 1, Smoking =
    2, U = 2, Mortality = 3), y = c(LBW = 3, Smoking = 2,
    U = 1, Mortality = 3))
drawdag(LBWsc1.DAG)
```



```
LBWsc2.DAG <- dagitty("dag {
Smoking -> LBW
LBW -> Mortality
Smoking -> Mortality
U -> LBW
U -> Mortality}")

coordinates(LBWsc2.DAG) <- list(x = c(LBW = 1, Smoking =
    2, U = 2, Mortality = 3), y = c(LBW = 3, Smoking = 2,
    U = 1, Mortality = 3))
drawdag(LBWsc2.DAG)
```



The variables of study are three: if the mother smokes or not, if the baby presents a low weight at the moment of birth, and if the baby survives the first month of life. Notice the shape of the graphs: if U is ignored, they are the same scenarios as presented in the common cause section. What medical studies suggest is that underweighted babies present less chances of survival than ordinary babies for multiple reasons: weight involves a better organ development, and indicates that there is certain fat that can be used for protection, warmth and energy. Experts also proclaim that if the mother smokes during the pregnancy, the baby development can be compromised, leading to miscarriage or fragile health $increasinginfantmortality$. But when 'smoking mother' and 'low birth weight' are implied in the same model, it seems that if the mother smokes during the pregnancy, and the baby has low weight at birth, she has less chances of dying.

In this example, there are unmeasured variables U that affect both low birth weight and mortality, though the only cause that we are accounting for is smoking. The questions that arise are: does smoking cause mortality? Does low birth weight cause mortality? We will simulate the data with the R package **simstudy**. We will increase the natural probabilities to visualize with clarity the issue. Let's assume that U is an unkown health condtion that can be absent 0 or present 1.

```
samplesize <- 10000
#Data for scenario 1
var.sc1 <- defData(varname = 'U', dist = 'binary',
    formula = 0.5)
var.sc1 <- defData(var.sc1, varname = 'Smoking', dist = '
    binary', formula = 0.5)
var.sc1 <- defData(var.sc1, varname = 'LBW', dist = '
    binary', formula = '0.5 * U + 0.4 * Smoking', link = '
    identity')
var.sc1 <- defData(var.sc1, varname = 'Mortality', dist =
     'binary', formula = '0.05 * Smoking + 0.95 * U', link
     = 'identity')
set.seed(13)
LBWsc1.df <- genData(samplesize, var.sc1)
#Data for scenario 2
var.sc2 <- defData(varname = 'U', dist = 'binary',
    formula = 0.5)
var.sc2 <- defData(var.sc2, varname = 'Smoking', dist = '
    binary', formula = 0.5)
var.sc2 <- defData(var.sc2, varname = 'LBW', dist = '
    binary', formula = '0.5 * U + 0.4 * Smoking', link = '
    identity')
var.sc2 <- defData(var.sc2, varname = 'Mortality', dist =
     'binary', formula = '0.01 * Smoking + 0.7 * U + 0.1 *
     LBW', link = 'identity')
```

```r
set.seed(13)
LBWsc2.df <- genData(samplesize, var.sc2)
```

5 Conclusion

6 References

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