Educational Note: Paradoxical Collider Effect in the Analysis of Non-Communicable Disease Epidemiological Data: a reproducible illustration and web application

Paradoxical effects due to conditioning on a third variable correlated with both exposure and outcome in the analysis of observational data is common but correlation is not causation

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1 Summary

In the epidemiological literature different explanations have been proposed to describe the paradoxical protective effect of established risk factors. A collider for a certain pair of variables (exposure and outcome) is a third variable that is influenced by both of them. Controlling for, or conditioning the analysis on (i.e., stratification or regression) a collider, can introduce a spurious association between its causes (exposure and outcome). Based on a motivating example in non-communicable disease epidemiology, we generated a dataset with 1,000 observations to contextualize the effect of conditioning on a collider. We estimate the effect of 24-hour dietary sodium intake in grams on systolic blood pressure in mmHg accounting for the effect of age in years to illustrate the paradoxical effect of 24-hour dietary sodium intake on systolic blood pressure after conditioning on a collider (24-hour urinary protein excretion in mg). If the main objective of an study is to obtain a predictive model that makes accurate predictions of the outcome researchers may probably condition on the collider to possibly increase the precision of the prediction. However, if the main objective is to create a model of reality that is useful in making decisions based on assumptions about the causal relationship of variables (a structural causal framework), then conditioning on the collider would introduce collider bias and probably paradoxical effects. We provide R-code in easy-to-read boxes throughout the manuscript and a GitHub repository: https://github.com/migariane/ColliderApp for reproducibility and an educational web application allowing real-time interaction to visualize the paradoxical effect of conditioning on a collider http://watzilei.com/shiny/collider/.

2 Key messages box

- Paradoxical associations between an outcome and exposure are common in epidemiological studies from observational data.
- A collider is a variable that is causally influenced by an exposure and an outcome.
- Controlling in multivariable analyses for a collider can introduce a spurious association between

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its causes (exposure and outcome).

- Using Directed Acyclic Graphs based on substantial clinical knowledge helps to identify colliders.
- Whether or not to adjust for a collider will depend on the main analytical interest i.e., predictive modeling approaches will condition on it to increase predictive accuracy while modeling approaches will not condition on it to prevent bias.

3 Introduction

During the last 30 years, classical epidemiology has focused on the control of confounding [1]. However, it is only recently that epidemiologists have started to focus on the bias produced by colliders and mediators in addition to confounders [2, 3]. In the epidemiological literature different explanations have been proposed to describe the paradoxical protective effect of established risk factors; such as, for example the protective effect of maternal smoking on infant mortality and the incidence of pre-eclampsia, namely the birthweight and the smoking pre-eclampsia paradoxes [4, 5]. Directed acyclic graphs (DAGs) help to visualize the assumed structural relationship of the variables under analysis. Using DAGs we can distinguish between i) biases resulting from lack of conditioning on common causes of exposure and outcome (confounding) (Figure 1A); ii) conditioning on intermediates variables (mediation) (Figure 1B) or iii) on common effects (collider bias) (Figure 1C) [6, 7]. Note that in Figure 1 the arrow ($\rightarrow$) from A to Y means that you assume A causes Y.

A collider for a certain pair of variables (outcome and exposure) is a third variable that is influenced by both of them. Controlling for, or conditioning the analysis on (i.e., stratification or regression) a collider, can introduce a spurious association between its causes (exposure and outcome) potentially explaining why the medical literature is full of paradoxical findings [8]. In DAG terminology, a collider is the variable in the middle of an inverted fork (i.e., variable W in A $\rightarrow$ W $\leftarrow$ Y) [9] (Figure 1C). While this methodological note will not close the vexing gap between correlation and causation it will contribute to the increasing awareness and the general understanding of colliders among applied epidemiologists.

The remainder of the methodological note is structured as follows: i) we demonstrate the statistical structure of the collider bias through a simulated data generation using a linear system of structural equations; ii) we then illustrate the effect of conditioning on a collider based on a realistic non-communicable disease epidemiology example (hypertension and dietary sodium intake); iii) we provide R-code in easy-to-read boxes throughout the manuscript and a GitHub repository: https://github.com/migariane/ColliderApp for reproducibility and iv) we provide readers with an educational web application allowing real-time interaction to visualize the paradoxical effect of conditioning on a collider http://watzilei.com/shiny/collider/.

4 Statistical structure of a collider

4.1 Reviewing confounding

Regression is the tool that epidemiologist generally use to answer questions in observational studies, many of which are causal in principle. Let's begin by reviewing what we mean by controlling for a confounder (W) when assessing the association between treatment or exposure (A) and an outcome (Y) via the following causal graph (Figure 1A). In the above diagram, W acts as a confounder distorting the perceived causal relationship between A and Y if unaccounted for. Thus, confounding introduces bias, but it can be controlled conditioning on the confounder by regression or stratification. We now review adjustment for confounding via a linear regression model. In Box 1 we show how to generate data consistent with the DAG from Figure 1A after which we run two different regression models. W is generated as a standard

normally randomly distributed variable with i.e. mean 0 ($\mu = 0$) and variance 1 ($\sigma^2 = 1$) 1. The generation of A was forced to depend on W plus a standard normal distributed random noise and Y is generated depending on both the A and W plus a standard normal randomly distributed noise. Note that the true simulated effect of A is 0.3. Then, we run unadjusted (fit1) and adjusted (fit2: adjusted for W) regression models of the effect of A on Y and visualize the linear fit of both models using the package visreg implemented in the statistical software R (R Foundation for Statistical Computing, Vienna, Austria).

Box 1

```
library(visreg)  # to visualize regression output
library(ggplot2) # to visualize regression output
N <- 1000
set.seed(777)
W <- rnorm(N)
A <- 0.5 * W + rnorm(N)
Y <- 0.3 * A + 0.4 * W + rnorm(N)
fit1 <- lm(Y ~ A)
fit2 <- lm(Y ~ A + W)
visreg(fit1, "A", gg = TRUE, line = list(col = "blue"),
       points = list(size = 2, pch = 1, col = "black")) + theme_classic()
```

Table 1 (columns 1, 2) shows the coefficients (A, W) from the fitted regression models helping us to illustrate and interpret the confounding effect. Note that our confounder W is the only variable that is exogenous, i.e., it is not dependent or generated from the outcome Y or the exposure A and is the only variable that can be specified independently of the other variables in the model. However, both A and Y depend on W and they are thus endogenous to the system of linear equations, i.e., depend or are generated from the outcome Y or the exposure A. Thus, it does not depend on A or Y. The first regression ignores W and incurs an upward bias in the coefficient of A (0.471). The second regression including the confounder W recovers the true value of the coefficient of A (0.3) with a beta coefficient for A of 0.289 while increasing the R-squared from 0.197 to 0.298. Thus, statistically speaking, adjusting for W improves the goodness of fit of the model (Figure 2A, Table 1: columns 1, 2).

4.2 Collider deconstruction

Unlike in Figure 1A where the causal arrow starts from W, in Figure 1C they now point towards W from A and Y. If we condition on W (i.e., regression or stratification), we will have created a collider bias, i.e. a spurious association between A and Y. Classically, to describe the effect of the collider bias we use the expression *association is not causation.* It means that the association on a multiplicative scale P(Y = 1| A = 1) / P(Y = 1 | A = 0) or similarly that P(Y = 1 | A = 1) - P(Y = 1 | A = 0) on an additive scale is not causation. Conditioning on the collider by regression or stratification introduces bias while ignoring the collider does not add bias. To emulate this scenario, in Box 2 we generate the data, again using a simple linear data generating mechanism. First, we simulate A as a standard normal randomly distributed variable. Y is forced to depend on A plus a standard normal noise but W is generated depending on both A and Y plus a standard normal random noise. Notice that A is now exogenous while W is endogenous. Then we fit the unadjusted model (fit3) excluding the collider and the model including the collider (fit4: collider model). Note that the true simulated coefficient of A is 0.3.

Box 2

```
library(visreg)
library(ggplot2)
N <- 1000
set.seed(777)
A <- rnorm(N)
Y <- 0.3 * A + rnorm(N)
W <- 1.2 * A + 0.9 * Y + rnorm(N)
```

```
fit3 <- lm(Y ~ A)
fit4 <- lm(Y ~ A + W)
visreg(fit3, "A", gg = TRUE, line = list(col = "red"),
       points = list(size = 2, pch = 1, col = "black")) + theme_classic()
```

Table 1 (columns 3, 4) shows the coefficient of A for unadjusted (fit3) and the coefficients A, W for the collider models (fit4). Unlike the previous section, the simpler regression without W approximately recovers the true coefficient of A (0.3) with a value of the beta coefficient for A of 0.326, while the regression adjusting for W is substantially biased (-0.416). The model which includes the collider (fit4) is not unequivocally inferior from a statistical point of view. For instance, the goodness of fit of the collider model increases significantly with an R-squared that is approximately 80 percentage points higher than the unadjusted model. However, conditioning on the collider W has paradoxically changed the direction of the association between A and Y (Figure 2B, Table 1: column 3).

Note that even if the collider changed the direction of the association, it still helps to predict Y given that it is part of the conditional expectation function E(Y|A,W). It is important to highlight that if you do not care about prediction and your main interest is understanding how the world works (i.e., causal) you should not condition on W. Subject-matter knowledge (i.e., plausible biological associations in clinical epidemiological settings) is mandatory in causal modeling approaches [10]. Thus, using DAGs to communicate causal structural relationships between variables helps identifying variables that act as a collider between treatment and outcome [9, 11, 12].

5 Motivating Example

5.1 Data generation

Based on a motivating example in non-communicable disease epidemiology, we generated a dataset with 1,000 observations to contextualize the effect of conditioning on a collider. Comorbidities are defined as the coexistence of disorders, in addition to a primary disease of interest, which are causally unrelated to the primary disease (e.g., cancer) [13]. High blood pressure is one of the most common comorbidities. Nearly 1 in 3 Americans suffer from high blood pressure and more than half do not have it under control [14]. Sustained levels of systolic blood pressure over time are associated with increased cardio-vascular morbidity and mortality [15]. Summative evidence shows that exceeding the recommendations for 24-hour dietary sodium intake in grams is associated with increased levels of systolic blood pressure (SBP) in mmHg [16]. Patients affected by high blood pressure are advised to decrease 24-hour dietary sodium intake but high SBP is associated with increasing age in years [16]. Thus, age is a confounder for the association between sodium intake and SBP. However, high levels of 24-hour excretion of urinary protein (proteinuria) are associated with sustained high SBP, advanced age and increased 24-hour dietary sodium intake. Therefore, as depicted in Figure 3, proteinuria acts as a collider (Figure 3).

We estimate the effect of 24-hour dietary sodium intake in grams on systolic blood pressure (SBP) adjusting for age. The objective of the illustration is to show the paradoxical effect of 24-hour dietary sodium intake on SBP after conditioning on a collider (proteinuria).

Box 3 shows the data generation for the simulation based on the structural relationship between the variables depicted on a DAG (Figure 3). We assumed that SBP increases with increasing age and dietary sodium intake. We also simulated 24-hour excretion of urinary protein as a function of age, SBP, and sodium intake. We assured that the range of values of the simulated data was biologically plausible and as close to reality as possible [17, 18]. Supplementary Table 1 shows the descriptive statistics (minimum, maximum, mean, median, first and third quartiles) for the generated data.

The simulation implies a linear relationship between the variables. Thus, the interpretation of the beta coefficients in the formulae of the code on box 3 is straightforward (i.e., Systolic blood pressure $= \beta_1 \times$ sodium $+ \beta_2 \times$ age $+ \varepsilon$; where $\beta_1 = 2.25$, $\beta_2 = 2.00$, and ε is standard normal distributed error).

Supplementary Figure 1 shows the functional form for each variable and the multivariable correlation matrix.

Box 3

```
generateData <- function(n, seed){
    set.seed(seed)
    Sodium_gr <- rnorm(n, 3.50, 0.50)
    Age_years <- Sodium_gr * 18 + rnorm(n)
    sbp_in_mmHg <- 2.25 * Sodium_gr + 2.00 * Age_years + rnorm(n)
    Proteinuria_in_mg  <- 0.90 * Age_years + 1.80 * sbp_in_mmHg + 3.50 *Sodium_gr + rnorm(n)
    data.frame(sbp_in_mmHg, Sodium_gr, Age_years, Proteinuria_in_mg)
}

ObsData <- generateData(n = 1000, seed = 777)
```

We fit three different models to evaluate the effect of age on SBP: i) unadjusted model, ii) model adjusted for age, iii) model adjusted for age and the collider (proteinuria). The model specifications are shown here below; in Box 4 we show how to fit and visualize the corresponding models in R.

Models fit specification:

$$\text{Systolic Blood Pressure} = \beta_0 + \beta_1 \times \text{Sodium in gr} + \varepsilon$$
$$\text{Systolic Blood Pressure} = \beta_0 + \beta_1 \times \text{Sodium in gr} + \beta_2 \times \text{Age in years} + \varepsilon$$
$$\text{Systolic Blood Pressure} = \beta_0 + \beta_1 \times \text{Sodium in gr} + \beta_2 \times \text{Age in years} + \beta_3 \times \text{Proteinuria in mg} + \varepsilon$$

Box 4

```
library(broom) # to visualize regression models output
library(visreg)
## Models Fit
fit0 <- lm(sbp_in_mmHg ~ Sodium_gr, data = ObsData);tidy(fit0)
fit1 <- lm(sbp_in_mmHg ~ Sodium_gr + Age_years , data = ObsData);tidy(fit1)
fit2 <- lm(sbp_in_mmHg ~ Sodium_gr + Age_years + Proteinuria_in_mg, data = ObsData);tidy(fit2)

## Models fit visualization
par(mfrow = c(1,3))
visreg(fit0, ylab = "SBP in mmHg", line = list(col = "blue"),
points = list(cex = 1.5, pch = 1), jitter = 10, bty = "n")
visreg(fit1, ylab = "SBP in mmHg", line = list(col = "blue"),
points = list(cex = 1.5, pch = 1), jitter = 10, bty = "n")
visreg(fit2, ylab = "SBP in mmHg", line = list(col = "red"),
points = list(cex = 1.5, pch = 1), jitter = 10, bty = "n")
```

5.2 Effect of conditioning on a collider

Table 2 shows the model coefficients and goodness of fit and Figure 4 shows the linear fit for the association between sodium and SBP for each of the three different models illustrating the effect of conditioning on a collider. The coefficient for the effect of sodium on SBP paradoxically becomes a protective risk factor (i.e., for one unit increase in sodium intake SBP decreases 0.7 mmHg). Likewise, the linear fit shown in Figure 4C (collider model) in comparison with the fits from the unadjusted and bivariate adjusted model (Figures 4A and 4B) changes the interpretation of the main effect of sodium dramatically. We also provide the link to a web application (http://watzilei.com/shiny/collider/) (Supplementary Figure 2) where users can dynamically modify the input values of the beta coefficients of the collider model for

the data generation process. The range of values of the slider input allows users to visualize the collider effect and revert it interactively. Very small values of the input slider for the coefficients of the model for the generation of the collider effect revert it while higher values create the collider effect.

6 Conclusion

We investigated a situation where adding a certain type of variable to a linear regression model, called a collider, biased regression coefficient estimates while still improving model fit. DAGs based on subject matter knowledge are vital for identifying colliders. Determining if a variable is a collider involves thinking critically about the true unobserved data generation process and the relationship between the variables in a real-world scenario [12, 19]. Then, the decision whether to include or exclude the variable in a regression model using observational data in epidemiology lies in the main interest of your modeling strategy (i.e., whether it is prediction or explanation/causation). If the main objective of a study is to obtain a predictive model that makes accurate predictions of Y (response) researchers probably may condition on the collider to possibly increase the precision of the prediction. However, if the main objective is to create a model of reality that is useful in making decisions based on a structural causal framework, then conditioning on the collider would introduce collider bias and probably paradoxical effects. To conclude, making causal inferences on the basis of observational data is very hard but if you have an explanatory variable W that could actually be caused by the response Y as well as the exposure or treatment A, then you probably are faced with a collider. Most research in epidemiology tries to explain how the world works (i.e., it is causal), thus to prevent paradoxical associations, epidemiologist probably should not condition on a collider.

Contributors and sources

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The article and Shiny application arise from the motivation to disseminate the principles of modern epidemiology among clinicians and applied researchers. MALF developed the concept, designed the study, carried out the simulation, analysed the data, and wrote the article. DRS and MALF developed the Shiny application. All authors interpreted the data and drafted and revised the manuscript, code for the manuscript, and code for the shiny application. All authors read and approved the final version of the manuscript. MALF is the guarantor of the article.

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8 Figures and Tables

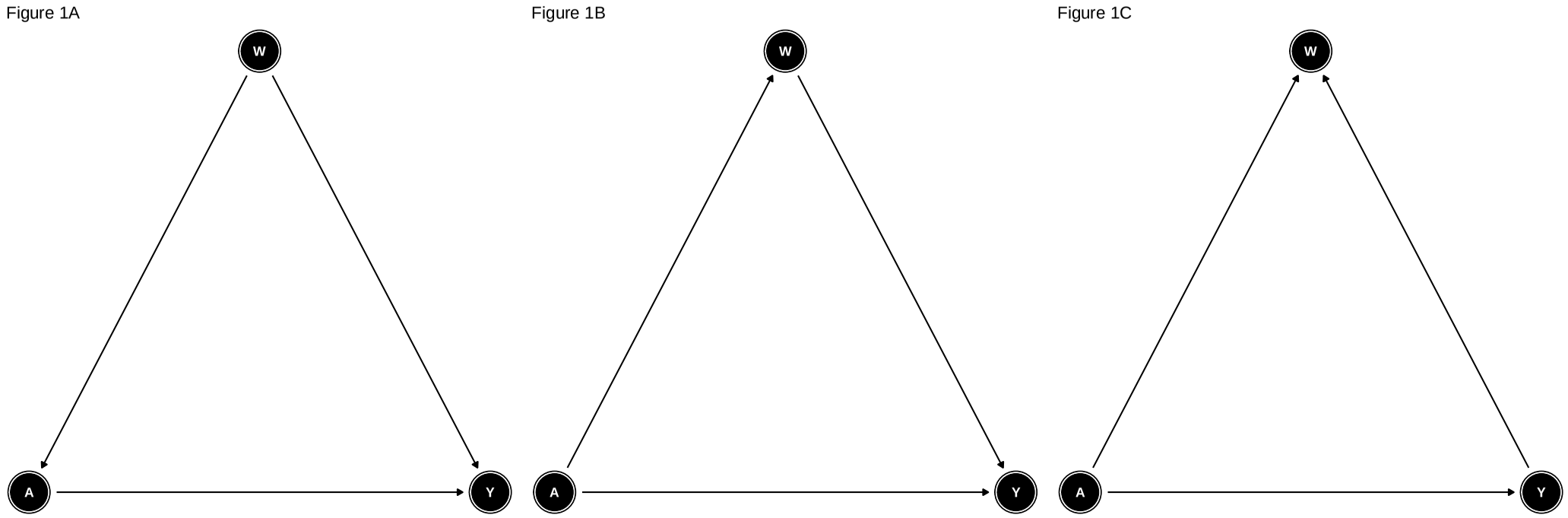


Figure 1: Basic structural associations between exposure and outcome: confounding (A), mediation (B) and collider (C)

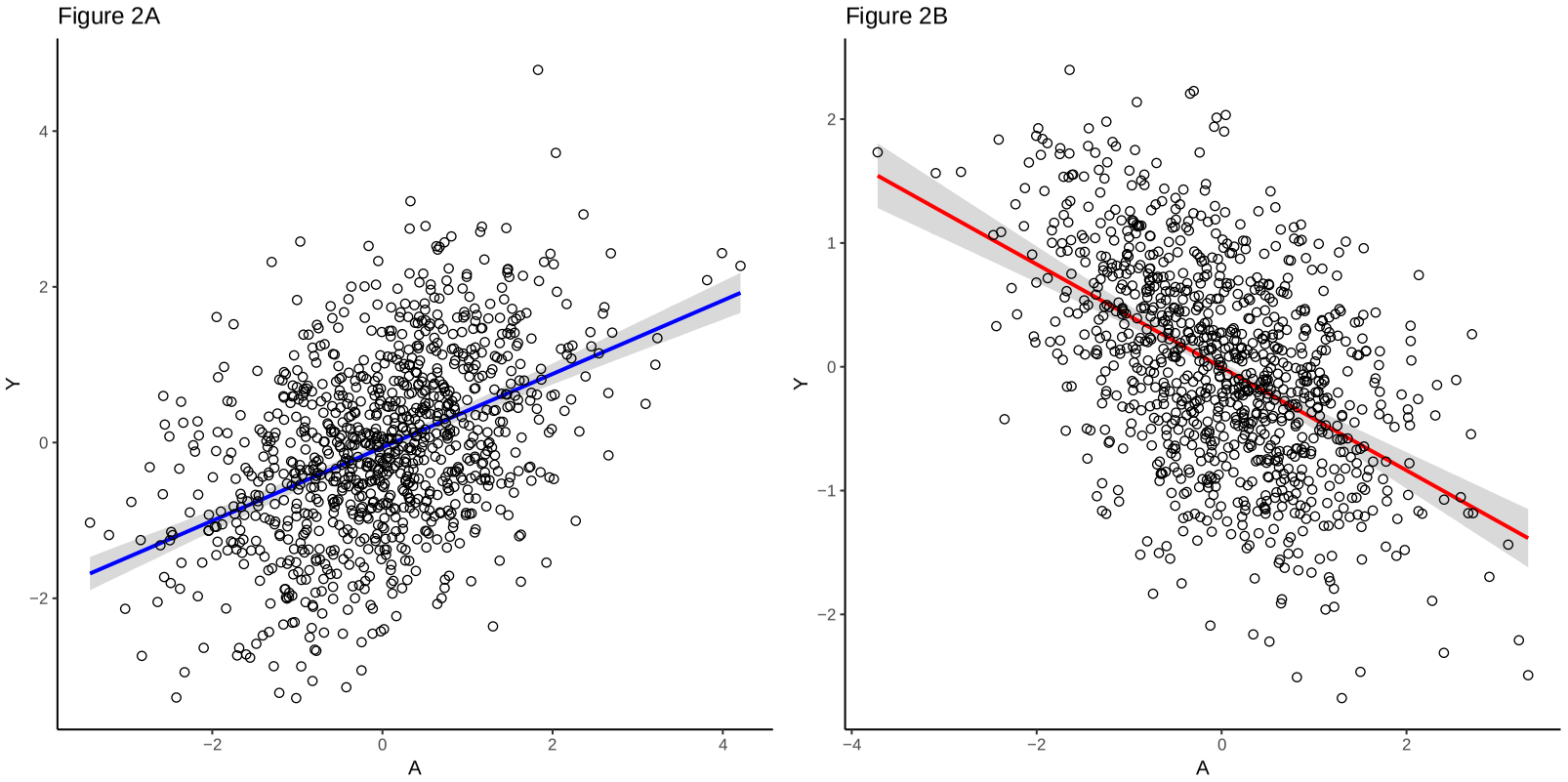


Figure 2: Visualization of the collider effect: Figure 2A model fit2 (Box 1) and Figure 2B model fit4 (Box 2), n = 1,000.

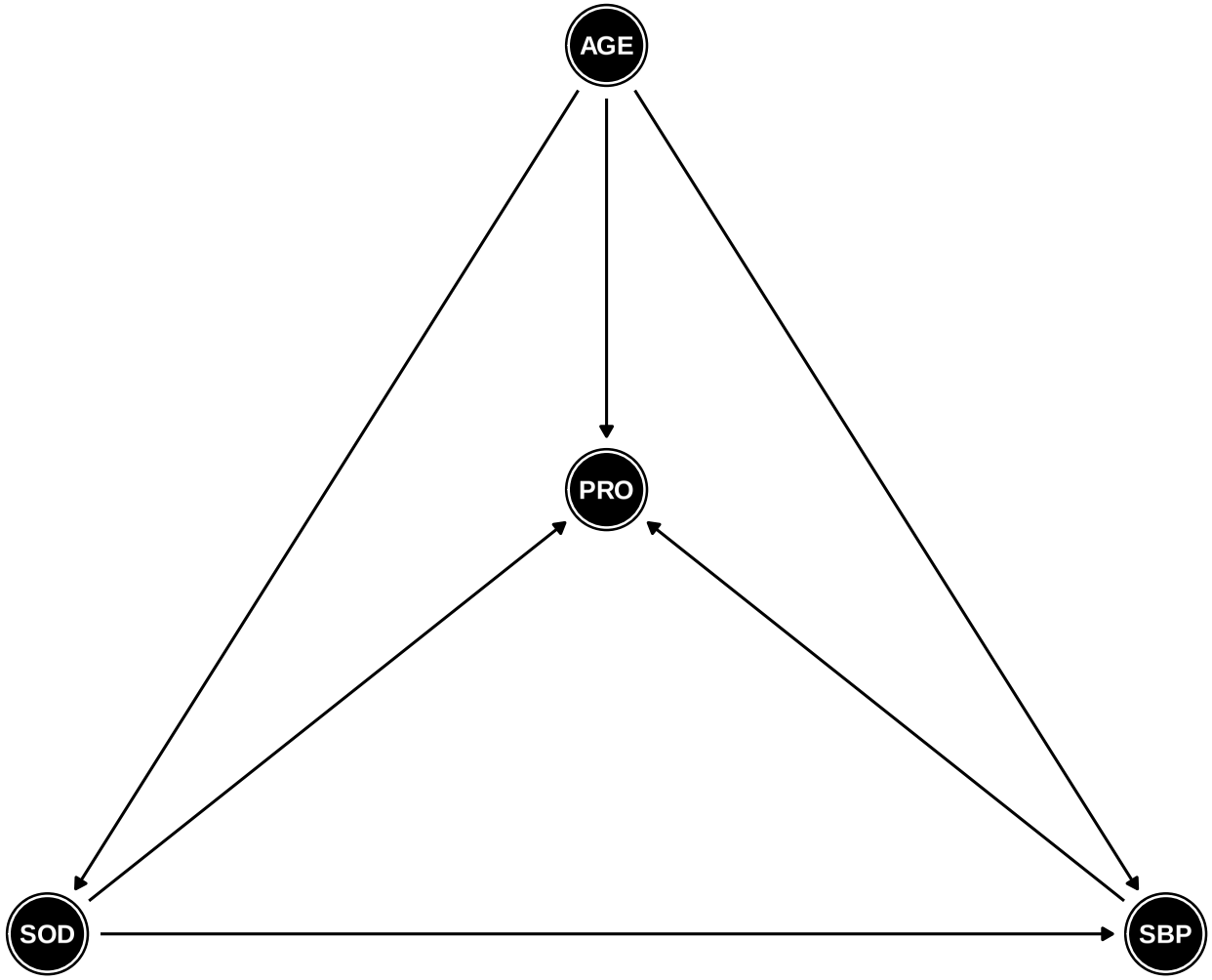


Figure 3: Directed acyclic graph depicting the structural causal relationship of the exposure and outcome, confounding and collider effects. Exposure: 24-hour sodium dietary intake in gr (SOD), outcome: systolic blood pressure in mmHg (SBP), confounder: age in years (AGE), collider: 24-hour urinary protein excretion, proteinuria (PRO)

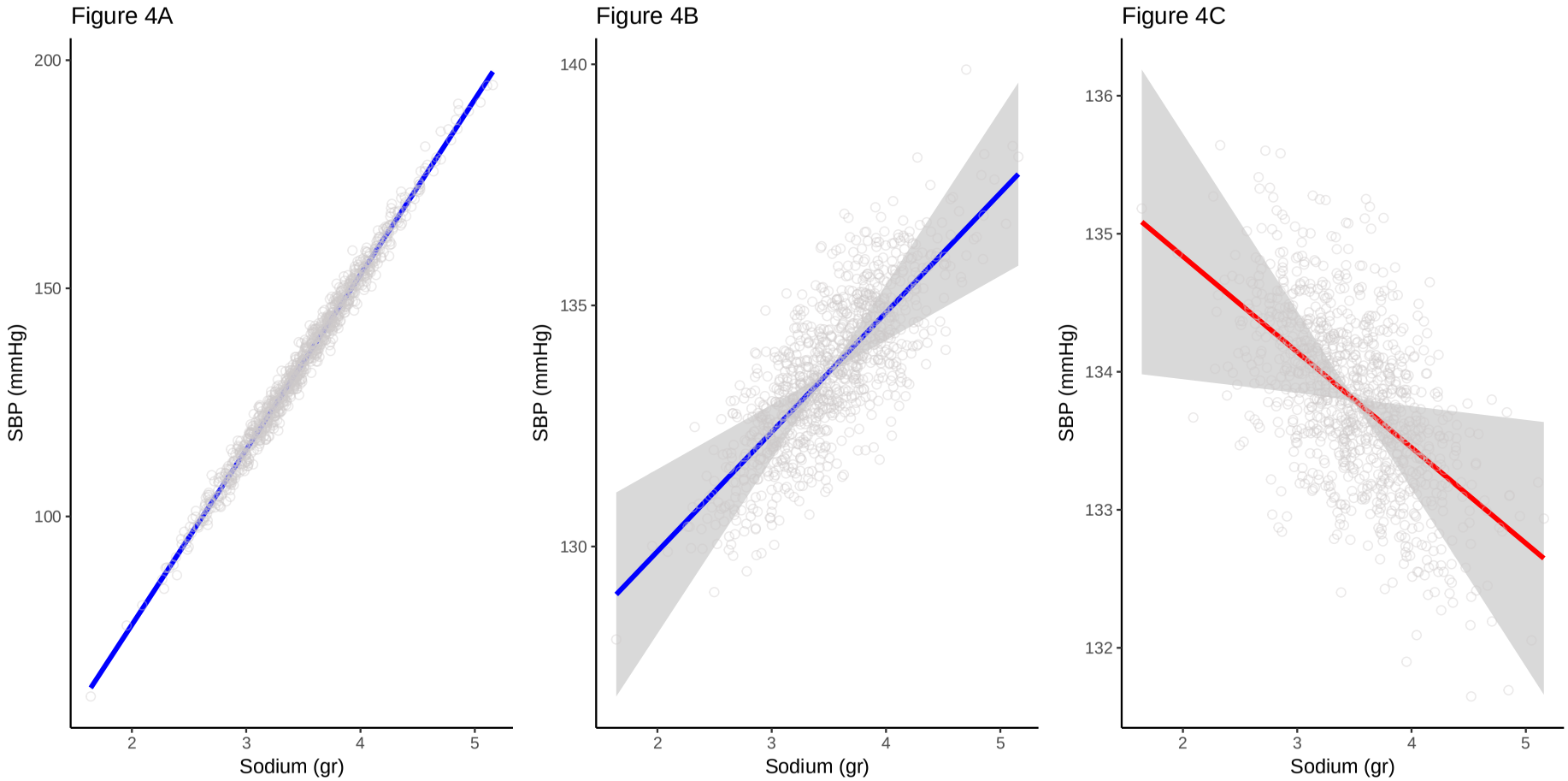
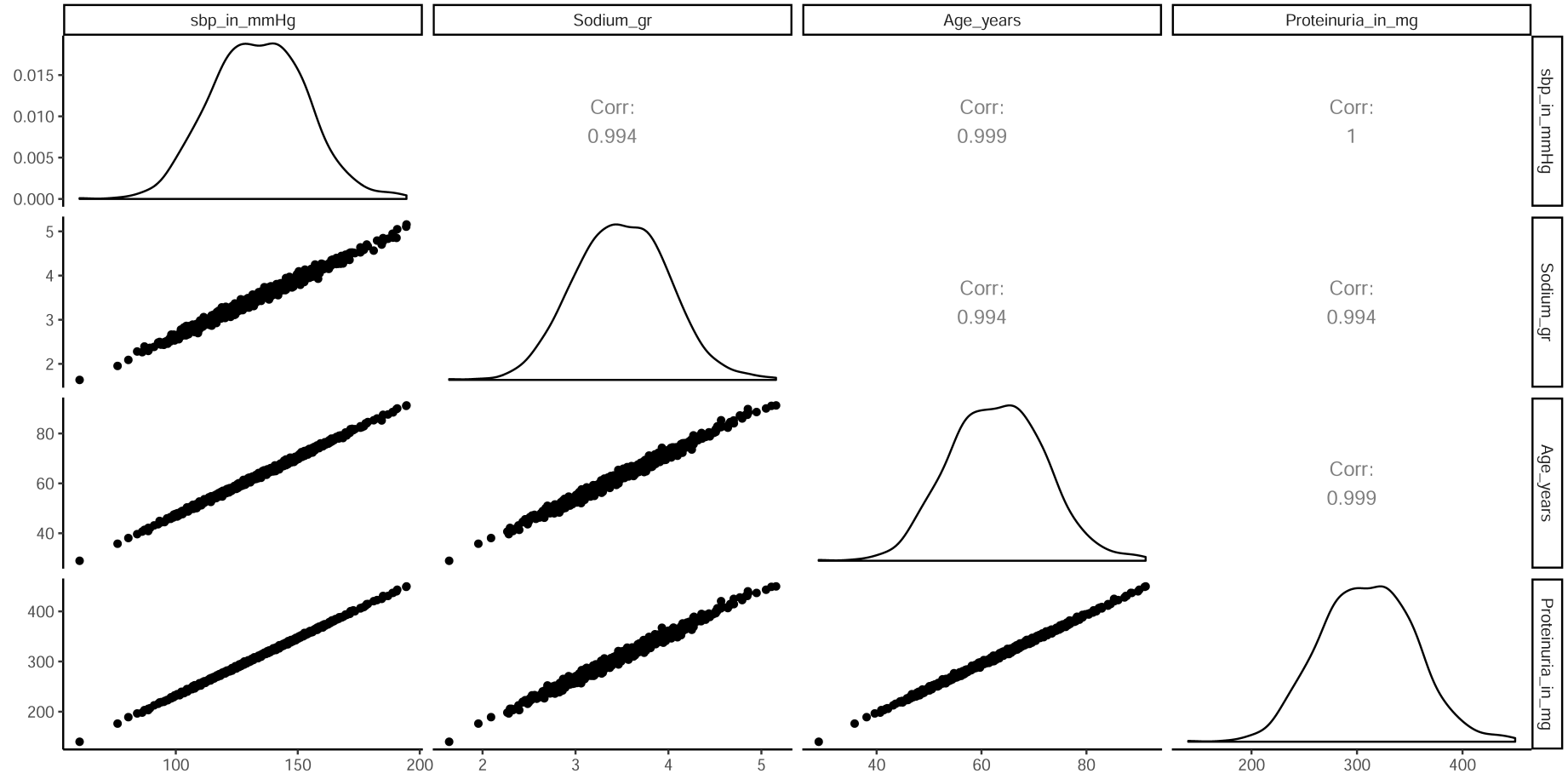
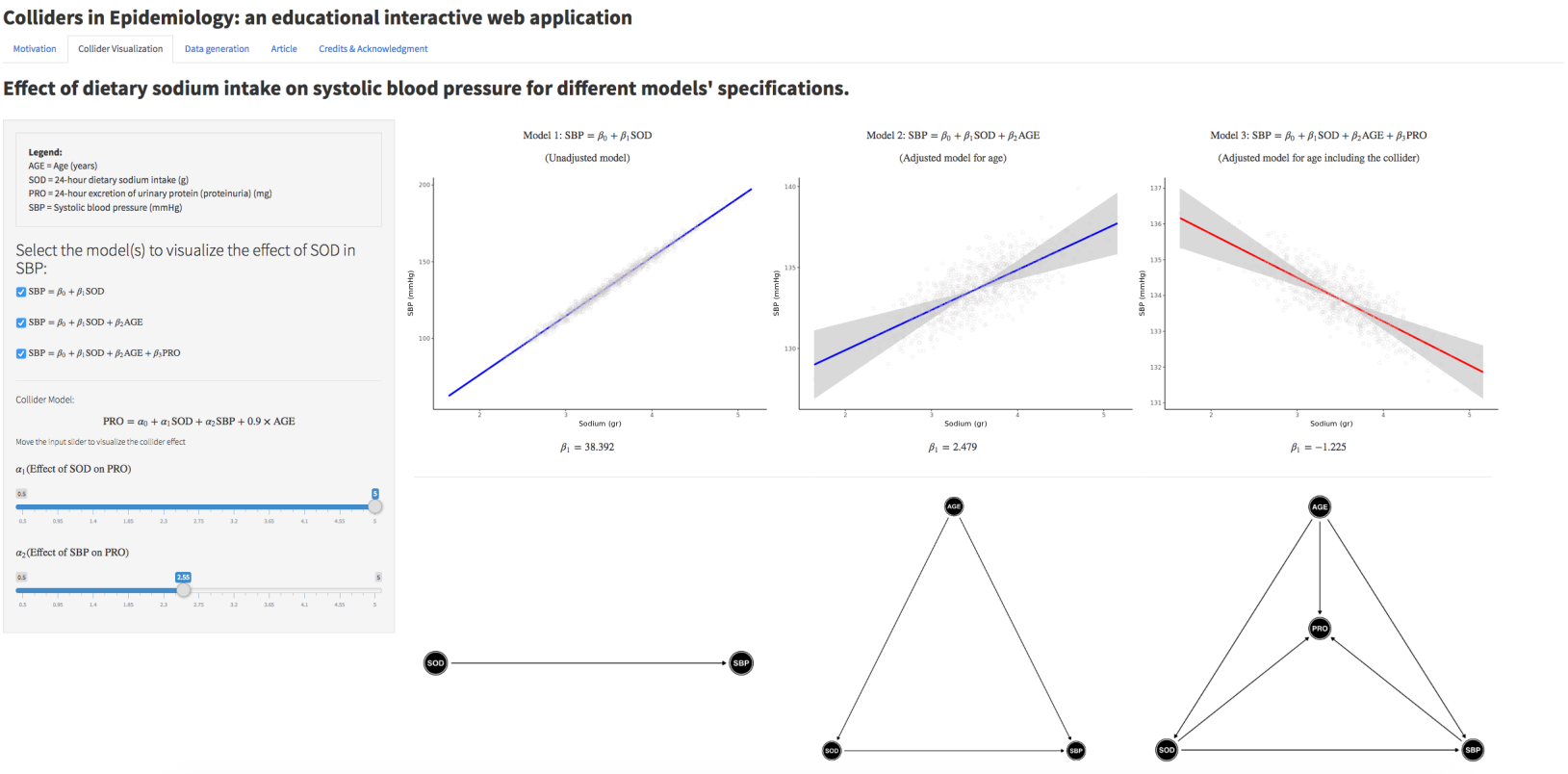


Figure 4: Collider effect for the illustration: Univariate (Figure 4A), bivariate (Figure 4B) and multivariate (Figure 4C) coefficients and standard errors for the linear association between systolic blood pressure and 24-hour sodium dietary intake adjusted for age acting as a confounder and proteinuria acting as a collider, n = 1,000



Supplementary Figure 1. Visualization of the multivariate structure of the data generation, n = 1,000



Supplementary Figure 2. Screenshot collider Shiny web application

Table 1: Coefficients and standard errors of the linear association between Y (outcome) and A (exposure) illustrating confounding and collider effects when adjusting for W, n = 1,000

	Dependent variable (Y):			
	W as confounder		W as collider	
	Unadjusted	Adjusted	Unadjusted	Adjusted
	(Fit1)	(Fit2)	(Fit3)	(Fit4)
A	0.471***	0.289***	0.326***	−0.416***
	(0.030)	(0.032)	(0.031)	(0.035)
W		0.425***		0.491***
		(0.035)		(0.018)
Constant	−0.061*	−0.060*	0.010	0.035
	(0.033)	(0.031)	(0.031)	(0.023)
Observations	1,000	1,000	1,000	1,000
R^2	0.197	0.298	0.101	0.493
Adjusted R^2	0.196	0.297	0.100	0.492
Residual Std. Error	1.050 (df = 998)	0.983 (df = 997)	0.972 (df = 998)	0.730 (df = 997)
F Statistic	245.138*** (df = 1; 998)	211.778*** (df = 2; 997)	111.585*** (df = 1; 998)	484.929*** (df = 2; 997)
Note:				*p<0.1; **p<0.05; ***p<0.01

Table 2: Univariate, bivariate and multivariate coefficients and standard errors for the linear association between systolic blood pressure and 24-hour sodium dietary intake adjusted for age acting as a confounder and proteinuria acting as a collider, n = 1,000

	Dependent variable (Y)		
	Systolic Blood Pressure in mmHg		
	(Univariate)	(Bivariate)	(Multivariate collider)
Sodium in gr	38.392***	2.479***	−0.693**
	(0.138)	(0.581)	(0.303)
Age in years		1.989***	0.103***
		(0.032)	(0.039)
Proteinuria in mg			0.419***
			(0.008)
Constant	−0.535	−0.195	−0.072
	(0.487)	(0.221)	(0.113)
Observations	1,000	1,000	1,000
R^2	0.987	0.997	0.999
Adjusted R^2	0.987	0.997	0.999
Residual Std. Error	2.168 (df = 998)	0.983 (df = 997)	0.502 (df = 996)
F Statistic	77,749.270*** (df = 1; 998)	191,223.900*** (df = 2; 997)	489,361.800*** (df = 3; 996)
Note:			*p<0.1; **p<0.05; ***p<0.01

Supplementary Table 1: Descriptive distribution of the simulated data, n = 1,000

Systolic blood pressure in mmHg	Sodium in gr	Age in years	Proteinuria mg in 24h
Min. : 60.55	Min. :1.640	Min. :28.96	Min. :140.0
1st Qu.:120.38	1st Qu.:3.157	1st Qu.:56.70	1st Qu.:278.5
Median :133.93	Median :3.491	Median :62.90	Median :309.8
Mean :133.87	Mean :3.501	Mean :63.03	Mean :310.0
3rd Qu.:147.16	3rd Qu.:3.835	3rd Qu.:69.24	3rd Qu.:341.1
Max. :194.55	Max. :5.158	Max. :91.28	Max. :449.9

9 Annex

```
library(visreg)
library(broom)
library(stargazer)

## Data Generation based on Noncommunicable Disease Epidemiology
generateData <- function(n, seed){
    set.seed(seed)
    Sodium_gr <- rnorm(n, 3.50, 0.50)
    Age_years <- Sodium_gr * 18 + rnorm(n)
    sbp_in_mmHg <- 2.25 * Sodium_gr + 2.00 * Age_years + rnorm(n)
    Proteinuria_in_mg  <- 0.90 * Age_years + 1.80 * sbp_in_mmHg + 3.50 *Sodium_gr + rnorm(n)
    data.frame(sbp_in_mmHg, Sodium_gr, Age_years, Proteinuria_in_mg)
}

ObsData <- generateData(n = 1000, seed = 777)

## Models Fit
fit0 <- lm(sbp_in_mmHg ~ Sodium_gr, data = ObsData);tidy(fit0)
fit1 <- lm(sbp_in_mmHg ~ Sodium_gr + Age_years , data = ObsData);tidy(fit1)
fit2 <- lm(sbp_in_mmHg ~ Sodium_gr + Age_years + Proteinuria_in_mg, data = ObsData);tidy(fit2)

## Models visualization
par(mfrow=c(1,3))
visreg(fit0, ylab = "SBP in mmHg", line=list(col="blue"),
 points = list(cex = 1.5, pch = 1), jitter = 10, bty = "n")
visreg(fit1, ylab = "SBP in mmHg", line=list(col="blue"),
 points = list(cex = 1.5, pch = 1), jitter = 10, bty = "n")
visreg(fit2, ylab = "SBP in mmHg", line=list(col="red"),
 points = list(cex = 1.5, pch = 1), jitter = 10, bty = "n")

## Comparing Models
stargazer(fit0, fit1, fit2, type = "latex", multicolumn = FALSE)
```

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