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# Modelos estructurales marginales para el control de sesgos en estudios observacionales con factores de riesgo y exposición tiempo-dependientes

Código en: [Q](#)

Seminario Métodos de Investigación en Salud Pública

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# Problemática

Estructura hipotética más cercana a lo real

Primera aproximación

Diagrama Causal  
Simplificado

Entonces...

## ► código

```
## Error in loadNamespace(i, c(lib.loc, .libPaths()), versionCheck = v[[i]]): namespace 'rlang' 0.4.12 is already loaded, but >= 1.0.1 is required
```

```
for (i in 1:nrow(data)){
  data$y3[i]<-base::sample(x=seq(from=data$y2[i]+1,to=22),1)
  data$y3[i]<-ifelse(data$y3[i]<=data$y2[i],22,data$y3[i])
  data$y3[i]<-ifelse(data$y3[i]>=23,22,data$y3[i])
  data$y4[i]<-ifelse(!is.na(data$y3[i]),base::sample(x=seq(from=data$y3[i]+1,to=22),1),22)
  data$y4[i]<-ifelse(data$y4[i]<=data$y3[i],22,data$y4[i])
  data$y4[i]<-ifelse(data$y4[i]>=23,22,data$y4[i])
}
```

```
## Error in 1:nrow(data): argument of length 0
```

```
set.seed(2125)
pac_aleatorio1<-sample(1:max(data$Paciente),40)
```

```
## Error in data$Paciente: object of type 'closure' is not subsettable
```

```
pac_aleatorio2<-setdiff(sample(1:max(data$Paciente),40), pac_aleatorio1)
```

```
## Error in data$Paciente: object of type 'closure' is not subsettable
```

```
set.seed(2125)
pac_aleatorio3<-unique(data$Paciente)[sample(1:length(data$Paciente),15)]
```

```
## Error in data$Paciente: object of type 'closure' is not subsettable
```

```
# Horizontal version, antes era 1985
```

```
end_plot<-20
```

```
fig_trans<-ggplot(data)
```

# Problemática

Estructura hipotética más cercana a lo real

Primera aproximación

Diagrama Causal  
Simplificado

Entonces...

Objetivo:

**Estimar el efecto de la modalidad de tratamiento por trastornos por uso de sustancias (ambulatorios vs. residenciales) a la base en la probabilidad de experimentar subsiguientes readmisiones a TUS**

Análisis propuestos en esa oportunidad:

$$\text{readmisión} \sim A_{1(\text{Modalidad base})} + X_{2(\text{Completa tto. base})} + \epsilon$$

$$2^{\text{da}} \text{ readmisión} \sim A_{1(\text{Modalidad base})} + L_{2(\text{Completa tto. base})} + L_{3(\text{Completa 2}^{\text{do}} \text{ tto.})} + L_4$$

$$3^{\text{era}} \text{ readmisión} \sim A_{1(\text{Modalidad base})} + L_{2(\text{Completa tto. base})} + L_{3(\text{Completa 2}^{\text{do}} \text{ tto.})} + L_4$$

$$4^{\text{ta}} \text{ readmisión} \sim A_{1(\text{Modalidad base})} + L_{2(\text{Completa tto. base})} + L_{3(\text{Completa 2}^{\text{do}} \text{ tto.})} + L_4$$

¿Cómo se reflejaría en un diagrama?

# Problemática

Estructura hipotética más cercana a lo real

Primera aproximación

Diagrama Causal Simplificado

Entonces...

## ► código

```
## Error in loadNamespace(i, c(lib.loc, .libPaths()), versionCheck = vl[[i]]): namespace 'rlang' 0.4.12 is already loaded, but >= 1.0.1 is required
```

```
edge_function <- ggdag:::edge_type_switch("link_arc")
```

```
## Error in loadNamespace(i, c(lib.loc, .libPaths()), versionCheck = vl[[i]]): namespace 'rlang' 0.4.12 is already loaded, but >= 1.0.1 is required
```

```
dag23_plot<-  
ggdag:::if_not_tidy_dagitty(tidy_dag23) %>% ggdag:::node_status() %>%  
ggplot2::ggplot(ggplot2::aes(x = x, y = y, xend = xend,  
yend = yend, color = status, shape=factor(adjusted)))+  
  
scale_adjusted() +  
ggdag:::breaks(c("exposure", "outcome", "latent")) +  
geom_dag_edges_arc(curvature = c(0.5, rep(0.26))) +
```

```
ggdag:::geom_dag_point(size = 16) +  
ggdag:::geom_dag_label_repel(ggplot2::aes_string(label = "label",  
fill = "status"), size = 4.88, col = "white",  
show.legend = FALSE) +  
theme_dag() +  
scale_shape_manual(values = c(15, 16), name = "Ajustado", labels = c("Sí", "No")) +  
scale_fill_manual(values = c("#003891", "#EF9D2F", "gray30"), name = "Estatus", na.value = "black", labels = c("Expo  
scale_color_manual(values = c("#003891", "#EF9D2F", "gray30"), name = "Estatus", na.value = "black", labels = c("Expo  
guides(linetype = "none", edge_alpha = "none", shape = "none")) +  
guides(color = guide_legend(override.aes = list(arrows = NULL))) + #, guide_colourbar(order = 1)
```

# Problemática

Estructura hipotética más cercana a lo real

Primera aproximación

Diagrama Causal  
Simplificado

Entonces...

- Varias puertas traseras sin cerrar, confusión residual, abandono/pérdida, sobreajuste, etc.
- El diseño y la estrategia analítica hasta el momento no permite responder a una pregunta causal de manera adecuada (muchos contrastes condicionales a la trayectoria de tratamientos y del mediador)
- Debiesen analizarse otras estrategias que capturen efectos longitudinales

¿Se puede responder a la pregunta de si haber asistido a tratamiento residencial a la base ( $A_0$ ) es beneficioso?, y si lo es, ¿qué régimen/estrategia es óptima o casi óptima? [2]

"In longitudinal studies with time-dependent confounding, identifying the structure allows us to detect situations in which stratification-based methods would adjust for confounding at the expense of introducing selection bias (p. 622)" [1]

# Objetivo

Este proyecto apunta a servir como un material introductorio sobre modelos estructurales marginales para el control de sesgos en estudios observacionales con factores de riesgo y/o exposición tiempo-dependientes.

- Se mostrará su estimación paso a paso y mediante un ejercicio reproducible.
- Se utilizará una base de datos simulada para ilustrar el proceso.

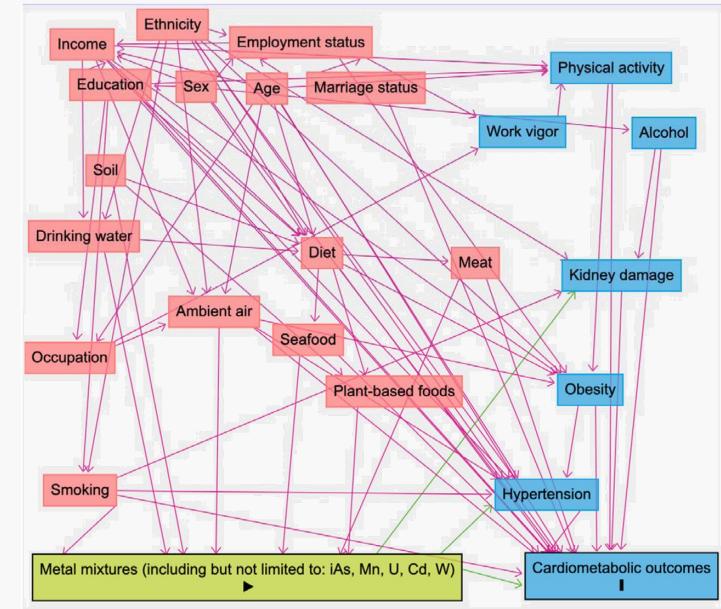
# Causalidad (1)

- Salud pública- epidemiología [3]
- Qué pasaría si... // Qué causa ... [4;5]



- Asociación vs. Causalidad [4;6]
- Inferencia [6]
- RCTs [7]
- Estudios observacionales

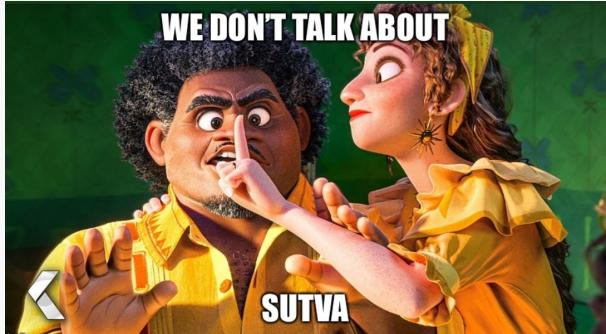
"It's much easier to get a result than it is to get an answer" [8]



Riseberg,E., Melamed, R., James, K., Alderete, T. & Corlin, L. (2021). Development and application of an evidence-based directed acyclic graph to evaluate the associations between metal mixtures and cardiometabolic outcomes. doi: <https://doi.org/10.1101/2021.03.05.21252993>

# Causalidad (2)

**SUTVA** [9;10;11]

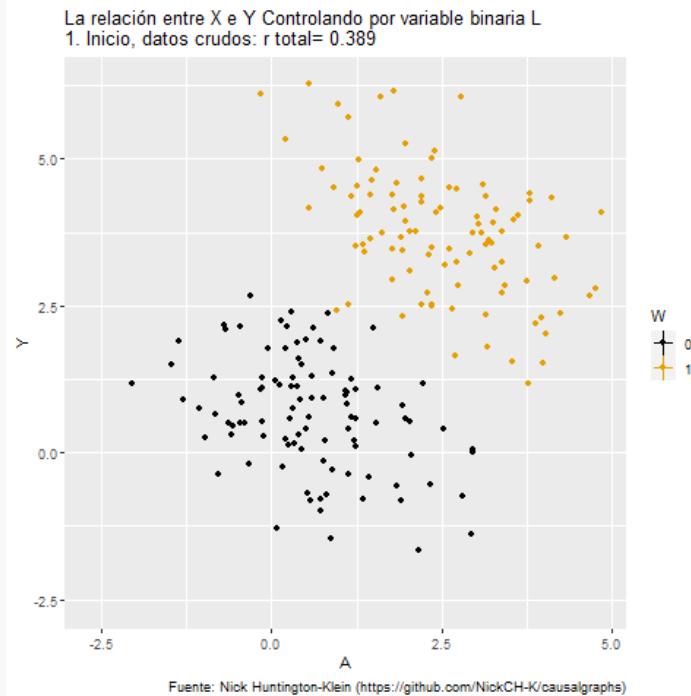


- *Consistencia*
- *Positividad*
- *Intercambiabilidad*

# Ajuste confusión



- **Estratificación / Regresiones**
- **Estandarización** [12;5;13]



# Marginal structural models

- ¿Por qué el nombre?
- Tres principales:
  - IPTW
  - Fórmula G paramétrica
  - Estimación G
- Ventajas y desventajas:

# Aplicación (1)

Se generó una base de datos de 1.000 observaciones con las siguientes características [14] :

- $t1 = \text{Tratamiento residencial Tiempo 0} (A_0) \sim \text{Bernoulli}(p=.23)$
  - $t2 = \text{Tratamiento residencial Tiempo 1} (A_1) \sim \text{Bernoulli}(p=.22)$
  - $t3 = \text{Tratamiento residencial Tiempo 2} (A_2) \sim \text{Bernoulli}(p=.15)$
  - $c1 = \text{Policonsumo} \sim \text{Bernoulli}(p=.32)$
  - $c2 = \text{Edad de inicio consumo de sustancias} \sim N(3,0.5)$
  - $dt1 = \text{Meses sin readmisión Primer tto.} \sim \text{Poisson}(\lambda=4)$
  - $dt2 = \text{Meses sin readmisión Segundo tto.} \sim \text{Poisson}(\lambda=3)$
  - $dt3 = \text{Meses sin readmisión Tercer tto.} \sim \text{Poisson}(\lambda=2)$
  - $v1 = \text{Confusor tiempo-dependiente (t1)} \sim 5 + 0.4\beta_{T\text{to residencial basal}} + 0.78\beta_{\text{Meses sin readmision 1}} + N(0, \sqrt{0.99})$
  - $v2 = \text{Confusor tiempo-dependiente (t2)} \sim 5 + 0.4\beta_{T\text{to residencial (2<sup>do</sup>)}} + 0.78\beta_{\text{Meses sin readmision 1}} + N(0, \sqrt{0.55})$
  - $v3 = \text{Confusor tiempo-dependiente (t3)} \sim 5 + 0.4\beta_{T\text{to residencial (3<sup>er</sup>)}} + 0.78\beta_{\text{Meses sin readmision 1}} + N(0, \sqrt{0.33})$

## ► código

## Error in loadNamespace(i, c(lib.loc, .libPaths()), versionCheck = v[[i]]): namespace 'rlang' 0.4.12 is already loaded, but >= 1.0.1 is required

```
#Primeros 4 filas
head(datos,4) %>%
  knitr::kable("html", caption="Muestra de la base de datos (Primeras 4 filas)") %>%
  kableExtra::kable_classic(bootstrap_options = c("striped", "hover"),font_size = 10)
```

# Aplicación (2)

## ► código

```
## Error in loadNamespace(i, c(lib.loc, .libPaths()), versionCheck = vl[[i]]): namespace 'rlang' 0.4.12 is already loaded, but >= 1.0.1 is required

edge_function <- ggdag:::edge_type_switch("link_arc")

## Error in loadNamespace(i, c(lib.loc, .libPaths()), versionCheck = vl[[i]]): namespace 'rlang' 0.4.12 is already loaded, but >= 1.0.1 is required

dag34_plot<-
ggdag:::if_not_tidy_dagitty(tidy_dag34) %>% ggdag:::node_status() %>%
  ggplot2::ggplot(ggplot2::aes(x = x, y = y, xend = xend,
                                yend = yend, color = status, shape=factor(adjusted)))+
  #edge_function()+
  scale_adjusted()+ ggdag:::breaks(c("exposure", "outcome", "latent"))+
  theme_dag()+
  geom_dag_edges_arc(curvature = c(rep(0,12),5,5,0,5,0,5,rep(0,9)))+ #14 y 16 de 24
  ggdag::geom_dag_point(size = 16)+
  ggdag::geom_dag_label_repel(ggplot2::aes_string(label = "label",
    fill = "status"), size = 4.88, col = "white",
    show.legend = FALSE)+

  scale_shape_manual(values = c(15, 16), name="Ajustado", labels=c("Sí", "No"))+
  scale_fill_manual(values = c("#003891", "#EF9D2F", "gray30"), name="Estatus",na.value="black", labels=c("Exposición", "Resultado"), limits = c('exposure', 'outcome'))+
  scale_color_manual(values = c("#003891", "#EF9D2F", "gray30"), name="Estatus",na.value="black", labels=c("Exposición", "Resultado"), limits = c('exposure', 'outcome'))+#E6E6E6
  guides(linetype="none", edge_alpha="none", shape="none")+
  guides(color=guide_legend	override.aes = list(arrow = NULL))+#,guide_colourbar(order = 1)
  theme(plot.caption = element_text(hjust = 0))+
  theme(legend.position = "bottom", aspect.ratio=6/10)+
  labs(caption="Nota. Ak= Modalidad (Residencial/Ambulatoria); dtk= Meses libre de readmisión;\n\nvk= Confusor tiempo-dependiente")

## Error in loadNamespace(i, c(lib.loc, .libPaths()), versionCheck = vl[[i]]): namespace 'rlang' 0.4.12 is already loaded, but >= 1.0.1 is required

dag34_plot
```

# Aplicación (3)

- Se estima una ponderación inversa al tratamiento que tiene en cuenta exposición y/o confusores tiempo-dependientes [15]

## ► código

```
## Error: package or namespace load failed for 'geepack' in loadNamespace(i, c(lib.loc, .libPaths()), versionCheck = vl[[i]]):  
## namespace 'rlang' 0.4.12 is already loaded, but >= 1.0.1 is required
```

```
library(survey)  
library(ipw)
```

```
## Error: package or namespace load failed for 'ipw' in loadNamespace(i, c(lib.loc, .libPaths()), versionCheck = vl[[i]]):  
## namespace 'rlang' 0.4.12 is already loaded, but >= 1.0.1 is required
```

```
library(reshape)  
library(MuMIn)
```

#Estimamos el modelo de probabilidad inversa con el numerador (elementos invariantes en el tiempo) y el denominador todos los confusores de interés.

```
w <- ipwtm(  
  exposure = t,  
  family = "binomial",  
  link = "logit",  
  # Time invariant stuff  
  numerator = ~ factor(policonsumo) + edad_ini,  
  # All confounders  
  denominator = ~ v + factor(policonsumo) + edad_ini,  
  id = id,  
  timevar=time,  
  type="first",  
  data = datos)
```

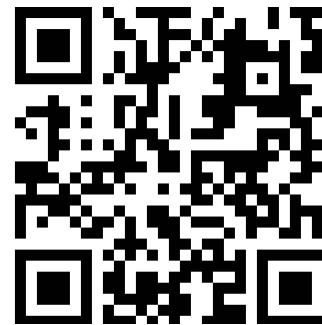
```
## Error in ipwtm(exposure = t, family = "binomial", link = "logit", numerator = ~factor(policonsumo) + : could not find function "ipwtm"
```

# Desafíos

- Structural Nested Models
- Confusores tiempo-modificados (*time-modified confounding*) [16]
- Generar modelos estructurales de análisis de supervivencia (incluir probabilidad inversa de censura)
- Variaciones
- Modelos doble o triplemente robustos
- Machine Learning (bagging, boosting, random forests, neural networks)

# Gracias!

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