# Dealing with time-varying confounding using SAS

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*PharmaSUG Single Day Event Tokyo 2018 on 4th September*

## Background

**Time-varying confounding** should be treated appropriately in observational research area, since choice of therapy in daily setting is usually affected by patient status, including treatment and covariate history. **CAUSALTRT procedure in SAS does NOT cover time-varying inverse probability weighting(IPW)** methods, while it handles non-time-varying IPW.

**Examples of SAS programming of time-varying IPW will be presented using simulation data** with background of the methodology.

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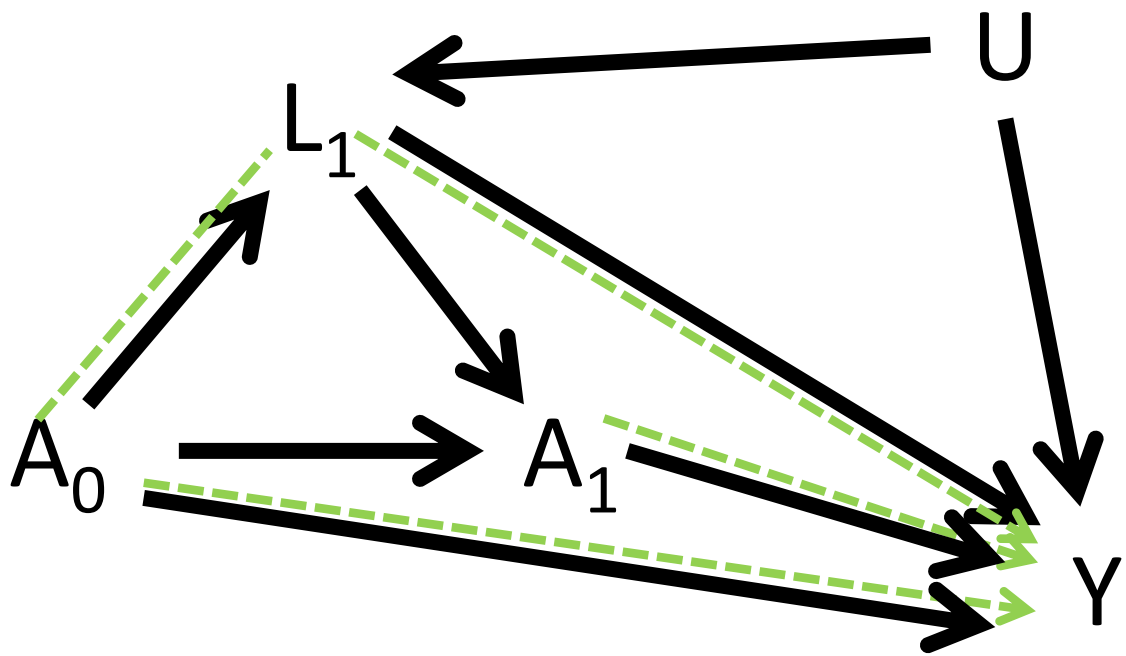
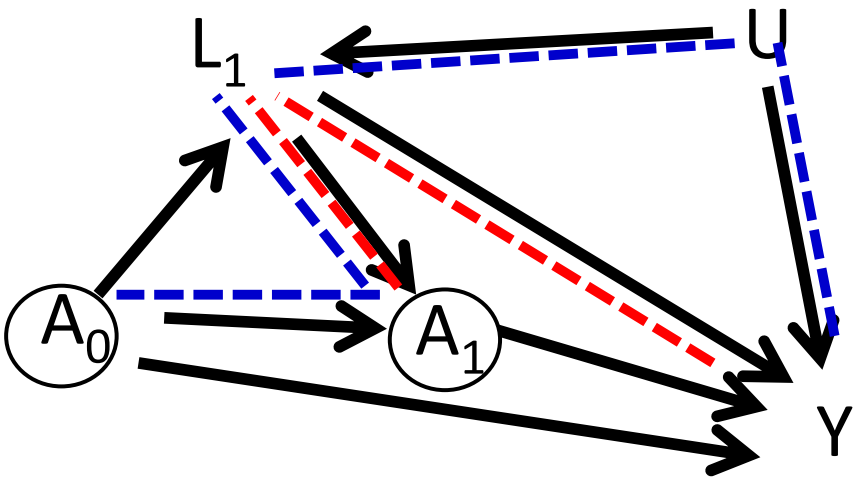
# Situation and Our Interest



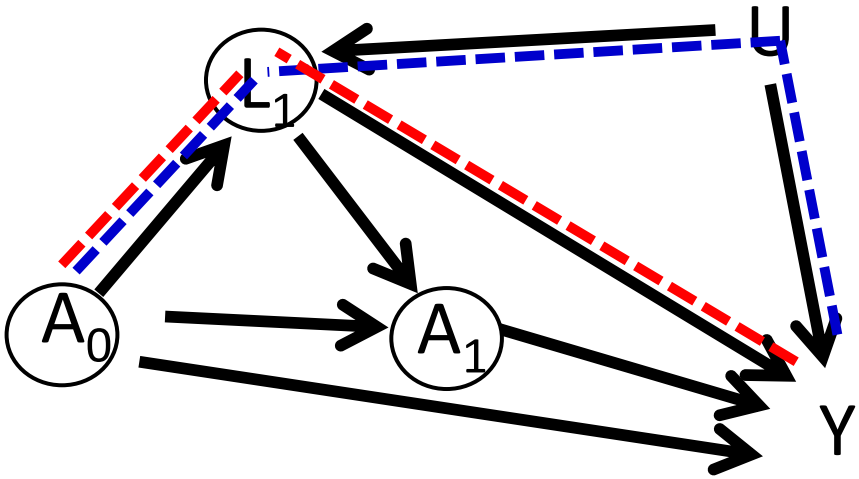

- Time-varying treatment A and covariate L, unmeasured confounder U
- **Our interest is to estimate joint causal effects of A(e.g. $E\left(Y^{(a_0, a_1)}\right)$),** which is total sum of green parts, where $E\left(Y^{(a_0, a_1)}\right)$ represents expected value of a potential outcome that would have been observed had the treatment been set to specific levels $a_0$ and $a_1$ .

# Why Traditional Methods Fail?

- Unconditioning on $L_1$, **neither effect of $A_0$ nor $A_1$ will be estimated without bias** because two paths(red and blue) open.




- Conditioning on $L_1$, **effect of $A_0$ will not be estimated without bias** because blue path opens and red path closes.




Note : Circled variables in DAG stand for conditioned(adjusted in model or stratified).

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# Theoretical background

- Identifiability conditions
  - Consistency.
    if $(A_0, A_1) = (a_0, a_1)$ for a given subject,
    then $Y^{(a_0,a_1)} = Y$ for that subject
  - Conditional exchangeability.
    $$Y^{(a_0,a_1)} \perp A_1 | L_1, A_0$$
    $$Y^{(a_0,a_1)} \perp A_0$$
  - Positivity.
    $$0 < f_{A_1|L_1,A_0}(A_1|L_1, A_0)$$
    $$0 < f_{A_0}(A_0),$$
    where *f* expresses (conditional) probability mass function

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- When our interest is counterfactual mean, i.e., $E\left(Y^{(a_0^*, a_1^*)}\right)$, where $(a_0^*, a_1^*)$ is treatment level of interest,

  we will show this is equivalent to $E\left(I\left(\bar{A} =\right.\right.$

Using the identifiability conditions, IPW mean of Y is:

$$\int I\left(\bar{A} = (a_0^*, a_1^*)\right) y \frac{f(y, a_0, a_1, l_1)}{f_{A_0}(a_0) f_{A_1|L_1,A_0}(a_1|l_1, a_0)} dy d\bar{a} dl_1$$

$$= \int y \frac{f(y, a_0^*, a_1^*, l_1)}{f_{A_0}(a_0^*) f_{A_1|L_1,A_0}(a_1^*|l_1, a_0^*)} dy dl_1$$

$$= \int y \frac{f_{Y|A_0,L_1,A_1}(y|a_0^*, l_1, a_1^*) f_{A_1|L_1,A_0}(a_1^*|l_1, a_0^*) f_{L_1|A_0}(l_1|a_0^*) f_{A_0}(a_0^*)}{f_{A_0}(a_0^*) f_{A_1|L_1,A_0}(a_1^*|l_1, a_0^*)} dy dl_1$$

$$= \int y f_{Y|A_0,L_1,A_1}(y|a_0^*, l_1, a_1^*) f_{L_1|A_0}(l_1|a_0^*) dy dl_1$$

$$= \int y^{(a_0^*, a_1^*)} f_{Y^{(a_0^*, a_1^*)}|A_0,L_1,A_1}\left(y^{(a_0^*, a_1^*)} \middle| a_0^*, l_1, a_1^*\right) f_{L_1|A_0}(l_1|a_0^*) dy^{(a_0^*, a_1^*)} dl_1$$

$$(\because \ consistency)$$

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$$= \int y^{(a_0^*,a_1^*)} f_{Y^{(a_0^*,a_1^*)}|A_0,L_1}\left(y^{(a_0^*,a_1^*)} \middle| a_0^*, l_1\right) f_{L_1|A_0}(l_1|a_0^*) dy^{(a_0^*,a_1^*)} dl_1$$

$$(\because \textit{conditional exchangeability } Y^{(a_0,a_1)} \perp A_1 | \, L_1, A_0)$$

$$= \int y^{(a_0^*,a_1^*)} f_{Y^{(a_0^*,a_1^*)},L_1|A_0}\left(y^{(a_0^*,a_1^*)}, l_1 \middle| a_0^*\right) dy^{(a_0^*,a_1^*)} dl_1$$

$$= \int y^{(a_0^*,a_1^*)} f_{Y^{(a_0^*,a_1^*)}|A_0}\left(y^{(a_0^*,a_1^*)} \middle| a_0^*\right) dy^{(a_0^*,a_1^*)}$$

$$= \int y^{(a_0^*,a_1^*)} f_{Y^{(a_0^*,a_1^*)}}\left(y^{(a_0^*,a_1^*)}\right) dy^{(a_0^*,a_1^*)} = E\left(Y^{(a_0^*,a_1^*)}\right)$$

$$(\because (\textit{conditional})\textit{exchangeability } Y^{(a_0,a_1)} \perp A_0)$$

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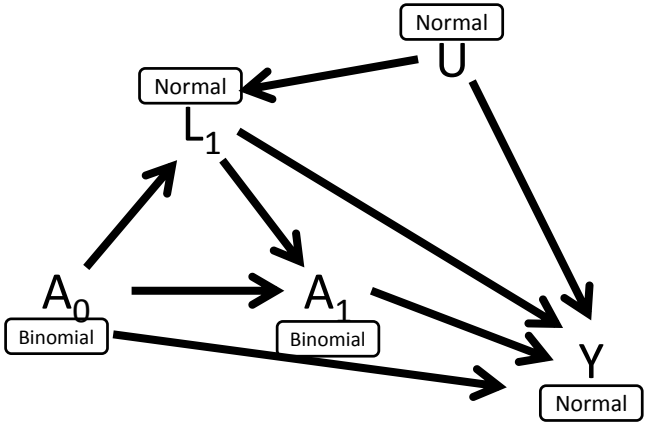
# Example (Traditional Methods vs IPW)

Simulation Data Generation

```
data ADSIM1 ;
  do USUBJID = 1 to 100 ;
    A0   = rand("Bernoulli",0.4) ;
    U    = rand("Normal",0,3) ;
    L1   = rand("Normal",0,1) + 2*A0 + 2*U ;
    P_A1 = exp(0.2 + 0.3*A0 + 0.2*L1)/(1 + exp(0.2 + 0.3*A0 + 0.2*L1)) ;
    A1   = rand("Bernoulli", P_A1) ;
    Y    = rand("Normal",0,1) + 3*A0 + 5*A1 + 2*L1 + 5*U ;
    output ;
  end ;
run ;
```

VIEWTABLE: Work.Adsim1

| | USUBJID | A0 | U | L1 | P_A1 | A1 | Y |
|---|---|---|---|---|---|---|---|
| 1 | 1 | 1 | 0.75 | 3.75 | 0.78 | 1 | 20.03 |
| 2 | 2 | 1 | -3.64 | -6.94 | 0.29 | 0 | -27.90 |
| 3 | 3 | 0 | -5.09 | -9.34 | 0.16 | 0 | -44.13 |
| 4 | 4 | 0 | 1.51 | 0.57 | 0.58 | 0 | 8.94 |
| 5 | 5 | 0 | 0.39 | 1.01 | 0.60 | 0 | 4.74 |
| 6 | 6 | 0 | -3.42 | -6.96 | 0.23 | 0 | -31.43 |
| 7 | 7 | 0 | -3.94 | -8.51 | 0.18 | 1 | -31.19 |
| 8 | 8 | 0 | 1.62 | 2.40 | 0.66 | 1 | 17.43 |




Note : The program generates normal response Y affected by A0, A1, L1(time-varying A and L) and unmeasured U.

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Analysis Programs

```
/*Unadjusted GLM(GLM1)*/
proc mixed data=ADSIM1 ;
    model Y = A0 A1 / s ;
run ;

/*Traditional adjusted GLM
(GLM2)*/
proc mixed data=ADSIM1 ;
    model Y = A0 A1 L1 / s ;
run ;
```

IPW

```
/*IPW_GLM*/
proc logistic data=ADSIM1 descending ;
    model A0 = ;
    output out=OUT0 p=P0 ;
run ;
proc logistic data=ADSIM1 descending ;
    model A1 = A0 L1 ;
    output out=OUT1 p=P1 ;
run ;
data OUT ;
    merge OUT0 OUT1 ;
    by USUBJID ;
    if A0=0 then P0=1-P0 ;
    if A1=0 then P1=1-P1 ;
    W=1/(P0*P1) ;
run ;
proc mixed data=OUT empirical ;
    model Y = A0 A1 / s ;
    weight W ;
    repeated Intercept / subject=USUBJID ;
run ;
```

Note : Sandwich variance estimator is calculated in order to take correlation of weighted(inflated) subject information into consideration.

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| N=100 | True Causal Effect | GLM1 (A0,A1) | GLM2 (A0,A1,L1) | IPW_GLM (weighted A0,A1) |
|---|---|---|---|---|
| joint(A0,A1) | **12** | 34.1 (6.83) | 3.14 (0.84) | 12.96 (9.03) |
| A0 | **7** | 3.54 (4.92) | -1.84 (0.59) | 6.09 (8.55) |
| A1 | **5** | 30.6 (5.02) | 4.98 (0.65) | 6.87 (4.92) |

| N=1,000 | True Causal Effect | GLM1 (A0,A1) | GLM2 (A0,A1,L1) | IPW_GLM (weighted A0,A1) |
|---|---|---|---|---|
| joint(A0,A1) | **12** | 34.2 (2.07) | 3.14 (0.25) | 12.17 (2.95) |
| A0 | **7** | 3.75 (1.57) | -1.86 (0.17) | 6.98 (3.35) |
| A1 | **5** | 30.5 (1.54) | 5.00 (0.20) | 5.19 (2.35) |

- 1,000 times simulation of N=100(upper table) , 1,000(lower table)
- Mean (SE) of estimates
- Causal effect of A0 equals to sum of direct effect of A0 -> Y(True value of 3) and indirect effect of A0 -> L1 -> Y(True value of 4).

# Summary

- **Weighted analysis using time-varying IPW was easily implemented with simple SAS codes**
- **Unbiasedness of time-varying IPW estimates was shown through the simulation**

# Note

- Stabilized IPW is also applicable
- As time points increase, some more efforts to calculate weight will be needed
- Same methodology is applicable to time to event outcome
- Application to Real World Data(RWD) would be expected in the future

# Reference


- Daniel RM, Cousens SN, De Stavola BL,Kenward MG, Sterneb JAC (2013) Methods for dealing with time-dependent confounding. *Statistics in Medicine 32*: 1584–1618
- Fitzmaurice G, Davidian M, Verbeke G, Molenberghs G (2009) Longitudinal Data Analysis. Chapman & Hall/CRC Taylor & Francis Group: Chapter 23
- Hernan MA, Robins JM (2017) Causal Inference. https://www.hsph.harvard.edu/miguel-hernan/causal-inference-book/
- 篠崎　智大(2017)『時間依存性交絡の調整』, 応用統計学会/計量生物学会年会チュートリアルセミナー
- 宮川　雅巳(2004)『統計的因果推論』, 朝倉書店


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