



Some examples of DAGs in published studies

Laust H Mortensen, LAMO@SUND.KU.DK Associate Professor, MS, PhD Department of Social Medicine University of Copenhagen



Example 1

ORIGINAL ARTICLE

Sex of the First-born and Risk of Preterm Birth in the Subsequent Pregnancy

Laust H. Mortensen,^{a,b} Henriette Svarre Nielsen,^c Sven Cnattingius,^d and Anne-Marie Nybo Andersen^a

Mortensen LH, Nielsen HS, Cnattingius S, Andersen AM. Sex of the First-born and Risk of Preterm Birth in the Subsequent Pregnancy. *Epidemiology* 2011; 22(3):328-32.



BACKGROUND

Recent data suggest that the chance of successfully maintaining a pregnancy may be influenced by the sex of previously born children.

The mechanism might be a maternal reaction to male-specific minor histocompatibility (HY) antigens



AIM

To explore a possible relation between sex of the first-born infant and the risk of preterm birth in the second pregnancy

METHODS

Using data from the National Medical Birth Registries in Denmark 1980-2004 and Sweden 1980-2001, we selected all women whose first and second births were singleton and who had information on sex of first-born infant and gestational age for the second (Denmark, n = 393,686; Sweden, n = 603,282). Cox proportional hazards regression analysis was used to estimate the hazard ratio of preterm birth in the second pregnancy according to the sex of the

first-born infant.





FIGURE 1. Distribution of gestational ages (histogram, right axis) and the percentage of second-born children having a boy as the older sibling (dots, left axis). The dotted line represents overall percentage of boys as the older sibling (51.4%).



RESULTS

TABLE 2. Hazard Ratios of Preterm Birth for the Secondborn if the First-born was a Boy in the Danish and Swedish Medical Birth Registries 1980–2003

Data	Crude HR (95% CI)	Adjusted HR (95% CI) ^a
Denmark	1.11 (1.06–1.16)	1.11 (1.06–1.16)
Sweden	1.09 (1.06–1.13)	1.09 (1.06-1.13)
Combined ^b	1.10 (1.07–1.13)	1.10 (1.07–1.13)

^aAdjusted for maternal age, interpregnancy interval and sex of the second-born infant.

^bThe combined estimates were calculated as a precision-weighted average of the log-hazard ratios.



CONCLUSION

Our initial conclusion: Robust assocation, likely causal.



BUT DURING PEER-REVIEW...

"Substantial quantities of data have been adduced to support the hypothesis that mammalian (including human) hormone levels affect the sex of the resulting offspring, high levels of testosterone being associated with the subsequent production of sons.

There is also ample evidence to suggest that testosterone levels may influence the risk of preterm birth, thus creating a completely spurious assocation between sex of the first born and preterm birth in the offspring "



BUT DURING PEER-REVIEW...

"Preterm birth is known to track strongly between pregnancies. Also, preterm birth is more likely to occur if the fetus at risk is a boy. The authors should adjust for preterm birth in the first pregnancy"

Exercise!



Expand this DAG to include

- 1) a factor U_1 that represents the innate testosterone levels (reviewer 1)
- 2) a factor U_2 that represents unobserved factors that cause preterm birth in both pregnancies (reviewer 2)

Use the association rules for DAG to judge if the reviewers' critiques might be correct





Expectations from the DAG via U1

- We examined whether the observed associations were a result of confounding by unobserved maternal factors (represented by U1 in Fig. 2) present at both the first and second pregnancy that affect sex ratio and the risk of preterm birth (eg, genes or innate sex hormone levels).
- We tested whether preterm birth in the first pregnancy predicted sex of the second-born infant, and whether sex of the first live birth predicted the sex of the second-born child.



Expectations from the DAG via U1

- A first preterm birth was associated with an odds ratio (OR) of **1.00** (95% CI 0.99 –1.02) for the second-born to be a boy.
- If the first-born was a boy, the OR for a second-born boy was also **1.00** (95% CI 0.99 –1.00).
- Whatever is causing the association between the sex of the first-born and preterm birth in the next pregnancy, it does not appear to be a factor that is present in both pregnancies.







Review 2

Adjustment for preterm birth in first pregnancy will open an otherwise closed pathway between fetal sex in the 1st pregnancy and preterm birth in the 2nd pregnancy through U2.

This is because preterm birth in the first pregnancy is a collider (collider stratification bias)



Review 1

The DAG suggest that

 U_1 is a potential confounder

 Sex_1 and sex_2 are associated though U_1

Preterm₁ and sex_2 are associated though U₁

Unlike U_1 , preterm and sex are observed, which means that the existence of U_1 can be tested in data!



Example 1: Summary

Drawing DAG can result in usefull predictions for the dataset

This may even be true in the presence of unmeasured factors

At any rate, remember that unmeasured factors should be considered in your DAG!

