Sex/Gender, COVID-19, and DAGs:
A 60-Minute Teaching Module for Introductory Epidemiology Lab

Developed as part of a Women, Gender, and Health independent study
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Introduction

This teaching example is intended for use in an introductory epidemiology course that includes topics in causal inference, specifically the use of directed acyclic graphs (DAGs). Commonly used in epidemiology since the 1990's, DAGs are graphical representations of causal relationships, and can be helpful in illustrating complex relationships between determinants of a health outcome, including exposures, mediators, and confounders.[1] This teaching example invites students to practice using DAGs to hypothesize relationships between sex, gender, and infectious disease mortality. Because this teaching example works best in a collaborative setting, it is encouraged that this example be taught in a lab or discussion section.

Background

Gender-disaggregated data of the COVID-19 pandemic has shown roughly the same caseload among men and women, but apparent increased risk of severe infection and mortality in men compared to women.[2] While this difference is seen across the globe, the size of the disparity varies widely between and within countries. In the U.S., for example, the gender difference varies widely between even neighboring states,[3] suggesting that these differences are not completely due to biological differences between males and females (sex), but also due to social circumstances and behavioral norms of men and women (gender). To clarify this distinction, 'sex' is a set of biological characteristics related to reproduction, and is distinct from 'gender', which refers to sociocultural conventions and norms of behavior for men and women. Though the two concepts are often conflated in medical and public health research, both sex *and* gender, independently and in tandem, influence health. These complex relationships have previously been illustrated using DAGs by Krieger for several health outcomes.[4]

This teaching method centers on a 2020 New York Times editorial piece by Heather Shattuck-Heidorn, Meredith Reiches and Sarah Richardson, directors of the GenderSci Lab at Harvard.[5] In the editorial, the authors use examples from the 1918 flu, SARS, and MERS epidemics to pose questions about the reasons for gender differences in COVID-19 mortality. Students will work in groups to illustrate three of the authors' claims using DAGs.

Attached Teaching Materials

1. Blank worksheet for distribution
2. Annotated worksheet with possible solutions and points for discussion

Students' Prior Knowledge

In order to get the most out of this teaching example, students should have a basic understanding of DAGs, including structural definitions of confounding and selection bias.

Learning Objectives for Students

1. Apply a gender-based analysis lens to infectious disease epidemiology
2. Strengthen understanding of DAGs (and their limitations) through complex examples

Teaching Method

1. (Optional) reading time: 10 minutes
    a. Students and teacher (lab TA and/or faculty) should read the attached editorial. This can be done as a homework assignment before class to remove in-class reading time.
2. Group work: 30 minutes
    a. Break into four groups
    b. Hand out worksheets: one problem for each group.
    c. Assign each group one of the three problems
    d. TA or faculty member should be available to answer questions and guide group work during this time.
3. Regroup and discuss: 30 minutes
    a. Each group spends 5 minutes presenting their scenarios and DAGs
    b. 10-minute wrap-up discussion
        i. Does someone want to share a challenge and/or success from their group work?
        ii. Did you discover any limitations to using DAGs to illustrate these scenarios?
        iii. What are the potential dangers of assuming that gender differences are completely biological in origin?

References

1. Greenland S, Pearl J, Robins JM. Causal Diagrams for Epidemiologic Research. *Epidemiology*. 1999;10(1):37-48.
2. The Sex, Gender and COVID-19 Project | Global Health 50/50. Accessed October 8, 2020. https://globalhealth5050.org/the-sex-gender-and-covid-19-project/
3. US Gender/Sex COVID-19 Data Tracker. GenderSci Lab. Accessed October 8, 2020. https://www.genderscilab.org/gender-and-sex-in-covid19
4. Krieger N. Genders, sexes, and health: what are the connections—and why does it matter? *International Journal of Epidemiology*. 2003;32(4):652-657. doi:10.1093/ije/dyg156
5. Shattuck-Heidorn H, Reiches MW, Richardson SS. Opinion | What's Really Behind the Gender Gap in Covid-19 Deaths? *The New York Times*. https://www.nytimes.com/2020/06/24/opinion/sex-differences-covid.html. Published June 24, 2020. Accessed August 21, 2020.

Group 1

Using DAGs to Understand Sex, Gender, and Infectious Disease

In today's lab, you will use DAGs to illustrate how sex and gender interact to influence infectious disease epidemiology. Some definitions: "Sex" is a set of biological characteristics related to reproduction, and is distinct from "gender", which refers to sociocultural conventions and norms of behavior for men and women. Each group will complete a set of problems based on four different excerpts from the New York Times Editorial you read for today—be prepared to share with the large group when you are finished!

Problem #1: 1918 Influenza Pandemic

"During the Spanish flu, men in the military and unskilled manual laborers working outside the home died at far higher rates than the general population, probably because they had less freedom to engage in social distancing; it's noteworthy that nonmilitary and upper-class males perished at rates similar to women overall. For similar social reasons — they were less able to social distance than women — men in 1918 already carried a significantly higher burden of tuberculosis relative to women when the pandemic began. This, when combined with influenza-induced pneumonia, proved deadly."

1. Using the information above, draw a DAG showing the association between influenza exposure and influenza mortality *among the working class.* Also include gender, occupation, and TB status in your DAG.

2. Based on your DAG in #1, would you consider gender as a possible confounder for the observed association between influenza infection and influenza mortality among the working class? What role does tuberculosis play in your DAG?

3. Now draw a DAG showing the association (or non-association) between influenza infection and mortality *among the upper class.* Also include occupation in your DAG.

4. Based on your DAG in #3, would you consider gender to be a confounder for the association between influenza infection and mortality among the upper class?

5. Now, draw a DAG for the association between gender and influenza mortality. Also include occupation and social class in your DAG.

6. Based on your work in the above questions and the information in the article, where would sex-linked biology fit (or not fit) in your DAGs? Choose one piece of evidence from the editorial to support your argument and be prepared to share with the class.

Group 2

Using DAGs to Understand Sex, Gender, and Infectious Disease

In today's lab, you will use DAGs to illustrate how sex and gender interact to influence infectious disease epidemiology. Some definitions: "Sex" is a set of biological characteristics related to reproduction, and is distinct from "gender", which refers to sociocultural conventions and norms of behavior for men and women. Each group will complete a set of problems based on four different excerpts from the New York Times Editorial you read for today—be prepared to share with the large group when you are finished!

Problem #2: 2003 Severe Acute Respiratory Syndrome (SARS)

"SARS emerged in early 2003 and quickly reached pandemic levels. Men overall indeed died at a higher rate than women. But a closer inspection of the data soon showed that sex differences varied considerably by age group…**The lower fatality rate among women was driven by particularly high infection rates among health care workers, who were predominantly young, healthy and female. So women were both disproportionately likely to be infected and disproportionately likely to survive, compared with men in that age group.** Among older women and men, and those with comorbidities such as heart disease, cancer, asthma and liver disease, there was little difference in SARS outcomes. The apparent sex difference was caused by gender-related occupational differences and diseases with complex, often socially rooted causes."

1. Using the above information about SARS mortality among younger people above in **bold**, draw a DAG showing the association between SARS infection and mortality. Also include gender (woman=1, man=0) and occupation (health care worker=1, other occupation=0). Assume that young women have better health than men, that is, that they have a lower risk of mortality.

2. Based on your DAG, would you consider gender to be a confounder for the association between SARS infection and mortality?

3. On your DAG above, indicate the direction of association between gender and occupation, and the direction of association between gender, healthy, and mortality.

4. Fatality rate is essentially the measured association between infection and mortality. Would you expect the crude fatality rate among younger people to be larger or smaller in absolute magnitude than the calculated fatality rate after adjusting for gender?

5. Based on the information given in the editorial, does sex-linked biology play a role in the fatality rate of SARS? Choose one piece of evidence from the article to back up your claim.

Group 3

Using DAGs to Understand Sex, Gender, and Infectious Disease

In today's lab, you will use DAGs to illustrate how sex and gender interact to influence infectious disease epidemiology. Some definitions: "Sex" is a set of biological characteristics related to reproduction, and is distinct from "gender", which refers to sociocultural conventions and norms of behavior for men and women. Each group will complete a set of problems based on four different excerpts from the New York Times Editorial you read for today—be prepared to share with the large group when you are finished!

Problem #3: Middle East Respiratory Syndrome

"MERS offers an even more clear-cut example. The disease overwhelmingly affected, and continues to affect, older men. Primary transmission from camels remains a key source of infections, and camel handling and slaughtering are predominantly male occupations in Saudi Arabia."

1. Based on the information above, draw a DAG for the association between gender (man = 1, woman = 0), occupation (camel handling = 1, other = 0) and MERS mortality.

2. Based on your DAG, would you consider occupation to be a confounder for the association between gender and MERS mortality?

3. Now, draw a DAG for the association between MERS exposure and MERS mortality. Include gender and sex-linked biology in your DAG (note that a DAG might have elements which are not connected to any other elements, indicating no association).

4. Based on your DAG from #3 and the information in the article, is gender (as a social variable) or sex (as a biological variable) more important for explaining why older men are disproportionately affected by MERS? Choose one piece of evidence supporting this claim to share out in the large group.

Group 4

Using DAGs to Understand Sex, Gender, and Infectious Disease

In today's lab, you will use DAGs to illustrate how sex and gender interact to influence infectious disease epidemiology. Some definitions: "Sex" is a set of biological characteristics related to reproduction, and is distinct from "gender", which refers to sociocultural conventions and norms of behavior for men and women. Each group will complete a set of problems based on four different excerpts from the New York Times Editorial you read for today—be prepared to share with the large group when you are finished!

Problem #4: COVID-19

"A key factor most likely related to male-female differences in Covid-19 fatalities is that men overall are in a poorer state of health than women. In a study examining sex differences in outcomes among Covid-19 patients in China, men were more likely than women to have any comorbidity or two or more of them. Of people with Covid-19 and chronic obstructive pulmonary disease, 83.3 percent were male. Of people with diabetes and cardiovascular disease, 58.9 percent and 62.1 percent, respectively, were male. To be sure, sex-linked biology may play a role in the development of some chronic diseases, but always in complex interaction with class, race or ethnicity, and gender-related variables. Several analyses have already demonstrated that in places where men have higher Covid-19 fatality rates than women, men also, on average, have far higher rates of behaviors such as smoking and comorbidities related to smoking, such as heart disease."

1. Draw a DAG for the association between gender (men = 1, women = 0) and COVID-19 mortality. Also include comorbidities (any comorbidities = 1, no comorbidities = 0).

2. Based on your DAG and the information in the editorial, would you consider comorbidities to confound the observed association between gender and COVID-19 mortality?

3. Though not mentioned in the article, there is some evidence that there are sex differences in innate immune response to coronaviruses (though the quality of evidence about this with respect to COVID-19 is poor). For the purposes of this exercise, let's assume that females have stronger innate immune response: that is, that they are less likely to die of COVID-19 once infected. Also assume that women are more likely to be exposed to COVID-19 due to occupational exposure. Draw a DAG for the association between COVID-19 exposure and mortality. Include sex, gender, and comorbidities in your DAG.

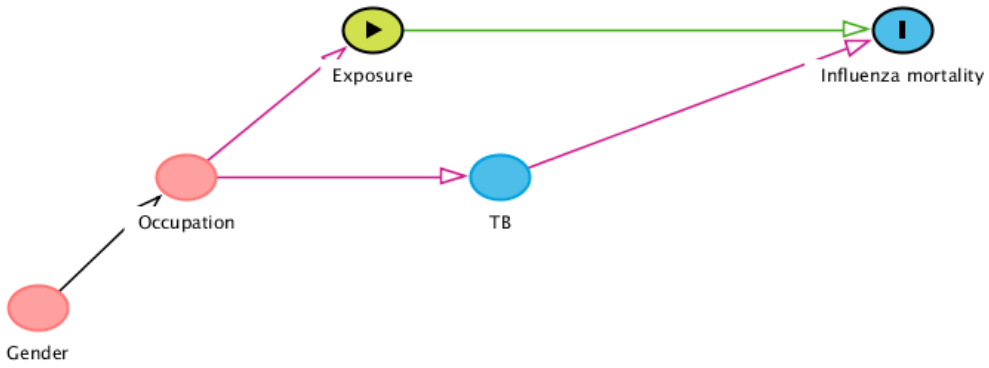
4. Based on the information in #3, would you consider sex-linked biology to modify the association between COVID-19 exposure and mortality? Does the DAG clearly illustrate this modification?

Possible Solutions – Problem #1

Problem #1: 1918 Influenza Pandemic

"During the Spanish flu, men in the military and unskilled manual laborers working outside the home died at far higher rates than the general population, probably because they had less freedom to engage in social distancing; it's noteworthy that nonmilitary and upper-class males perished at rates similar to women overall. For similar social reasons — they were less able to social distance than women — men in 1918 already carried a significantly higher burden of tuberculosis relative to women when the pandemic began. This, when combined with influenza-induced pneumonia, proved deadly."

1. Using the information above, draw a DAG showing the association between influenza exposure and influenza mortality *among the working class.* Also include gender, occupation, and TB status in your DAG.



2. Based on your DAG in #1, would you consider gender as a possible confounder for the observed association between influenza exposure and mortality among the working class? What role does tuberculosis play in your DAG?

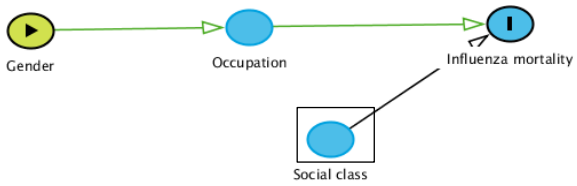
   Based on my DAG, gender is not a confounder between influenza exposure and mortality, except through its association with occupational exposure hazards. Tuberculosis is a mediator on the path from occupation to mortality.

3. Now draw a DAG showing the association (or non-association) between influenza exposure and influenza mortality *among the upper class.* Also include occupation in your DAG.

4. Based on your DAG in #3, would you consider gender to be a confounder for the association between exposure and mortality among the upper class?

   Based on my DAG, I would not consider gender (or occupation) as a confounder among the upper class for the association between flu exposure and mortality.

5. Now, draw a DAG for the association between gender and influenza mortality. Also include occupation and social class in your DAG. Does this DAG alone communicate the fact that mortality rates differed by gender among the lower class, but not among the upper class?



   No, this DAG does not to a good job on its own communicating how the association between gender and flu mortality differs between social classes. This DAG highlights the difficulties of illustrating effect measure modification in DAGs.

6. Based on your work in the above questions and the information in the article, where would sex-linked biology fit (or not fit) in your DAGs? Choose one piece of evidence from the editorial to support your argument and be prepared to share with the class.

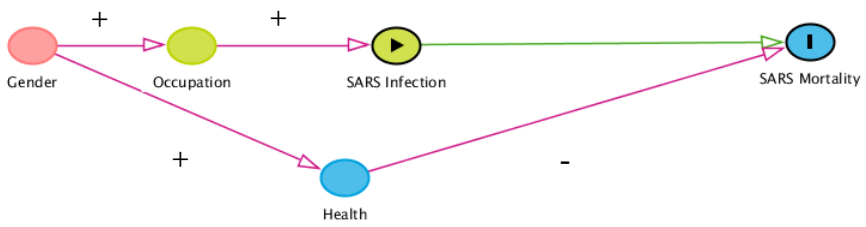
   No—the editorial only mentions social (gendered) differences in exposure and comorbidity (TB)

Possible Solutions – Problem #2

Problem #2: 2003 Severe Acute Respiratory Syndrome (SARS)

"SARS emerged in early 2003 and quickly reached pandemic levels. Men overall indeed died at a higher rate than women. But a closer inspection of the data soon showed that sex differences varied considerably by age group…**The lower fatality rate among women was driven by particularly high infection rates among health care workers, who were predominantly young, healthy and female. So women were both disproportionately likely to be infected and disproportionately likely to survive, compared with men in that age group.** Among older women and men, and those with comorbidities such as heart disease, cancer, asthma and liver disease, there was little difference in SARS outcomes. The apparent sex difference was caused by gender-related occupational differences and diseases with complex, often socially rooted causes."

1. Using the above information about SARS mortality among younger people above in **bold**, draw a DAG showing the association between SARS infection and mortality. Also include gender (woman=1, man=0) and occupation (health care worker=1, other occupation=0). Assume that young women have better health than men, that is, that they have a lower risk of mortality.



2. Based on your DAG, would you consider gender to be a confounder for the association between SARS infection and mortality?

   Yes, I would consider gender to confound the association between SARS infection and mortality because it creates a backdoor path of association (by way of occupation and health) between infection and mortality.

3. On your DAG above, indicate the direction of association between gender and occupation, and the direction of association between gender, healthy, and mortality.

4. Fatality rate is essentially the measured association between infection and mortality. Would you expect the crude fatality rate among younger people to be larger or smaller in absolute magnitude than the calculated fatality rate after adjusting for gender?

   By way of health, gender has a negative association with mortality among younger people and, by way of occupation, a positive association with SARS infection. Therefore I would expect the crude fatality in the entire population of young people to be an *underestimation* of the true (adjusted) fatality rate after gender is taken into account.

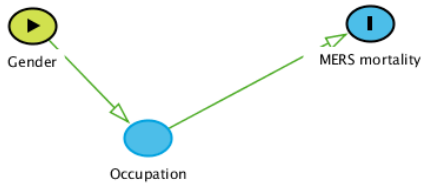
5. Based on the information given in the editorial, does sex-linked biology play a role in the fatality rate of SARS? Choose one piece of evidence from the article to back up your claim.

   The editorial and the DAGs above emphasize socialized gender differences rather than biological sex differences in SARS mortality.

Possible Solutions – Problem #3

Problem #3: Middle East Respiratory Syndrome
"MERS offers an even more clear-cut example. The disease overwhelmingly affected, and continues to affect, older men. Primary transmission from camels remains a key source of infections, and camel handling and slaughtering are predominantly male occupations in Saudi Arabia."

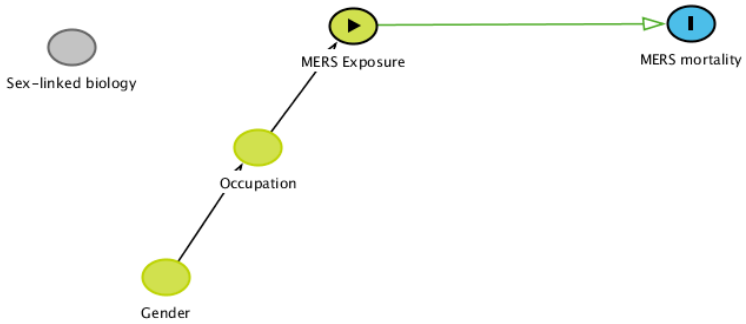
1. Based on the information above, draw a DAG for the association between gender (man = 1, woman = 0), occupation, (camel handling = 1, other = 0) and MERS mortality.



2. Based on your DAG, would you consider occupation to be a confounder for the association between gender and MERS mortality?

   Based on my DAG, occupation is a mediator, not a confounder, on the association between gender and MERS mortality.

3. Now, draw a DAG for the association between MERS exposure and MERS mortality. Include gender and sex-linked biology in your DAG (note that a DAG might have elements which are not connected to any other elements, indicating no association).



4. Based on your DAG from #3 and the information in the article, is gender (as a social variable) or sex (as a biological variable) more important for explaining why older men are disproportionately affected by MERS? Choose one piece of evidence supporting this claim to share out in the large group.

   Based on information from the editorial, MERS disproportionately affects older men in Saudi Arabia because they are disproportionately exposed due to a gendered distribution of labor. There is no evidence in the article about sex-linked biology influencing MERS mortality.

Possible Solutions – Problem #4

Problem #4: COVID-19

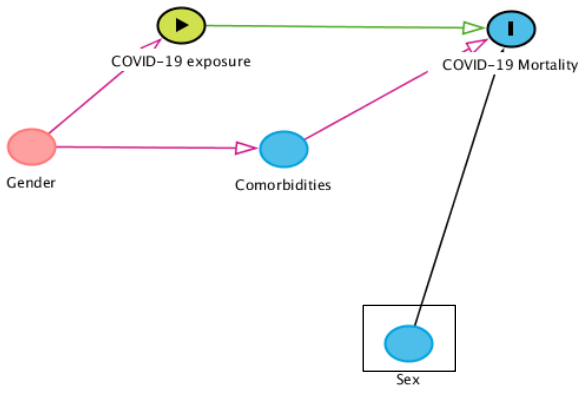
"A key factor most likely related to male-female differences in Covid-19 fatalities is that men overall are in a poorer state of health than women. In a study examining sex differences in outcomes among Covid-19 patients in China, men were more likely than women to have any comorbidity or two or more of them. Of people with Covid-19 and chronic obstructive pulmonary disease, 83.3 percent were male. Of people with diabetes and cardiovascular disease, 58.9 percent and 62.1 percent, respectively, were male. To be sure, sex-linked biology may play a role in the development of some chronic diseases, but always in complex interaction with class, race or ethnicity, and gender-related variables. Several analyses have already demonstrated that in places where men have higher Covid-19 fatality rates than women, men also, on average, have far higher rates of behaviors such as smoking and comorbidities related to smoking, such as heart disease."

1. Draw a DAG for the association between gender (men = 1, women = 0) and COVID-19 mortality. Also include comorbidities (any comorbidities = 1, no comorbidities = 0).

2. Based on your DAG and the information in the editorial, would you consider comorbidities to confound the observed association between gender and COVID-19 mortality?

   No—comorbidities are a mediator between gender and COVID-19 mortality.

3. Though not mentioned in the article, there is some evidence that there are sex differences in innate immune response to coronaviruses (though the quality of evidence about this with respect to COVID-19 is poor). For the purposes of this exercise, let's assume that females have stronger innate immune response: that is, that they are less likely to die of COVID-19 once infected. Also assume that women are more likely to be exposed to COVID-19 due to occupational exposure. Draw a DAG for the association between COVID-19 exposure and mortality. Include sex, gender, and comorbidities in your DAG.



4. Based on the information in #3, would you consider sex-linked biology to modify the association between COVID-19 exposure and mortality? Does the DAG clearly illustrate this modification?

   Yes, if there are differences in innate immune response between males and females (emphasis on *if*), then sex modifies the association between COIVD-19 exposure and outcome.