RESEARCH METHODS FOR CLINICAL INVESTIGATORS
Session 2:

What am I Estimating during a Study: Measure of Association or Causation?

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Objectives

At the end of the presentation, the audience will be able to:

- Define the differences between measure of association and causation
- List the measures of associations
- Interpret the measures of association

What's the Difference

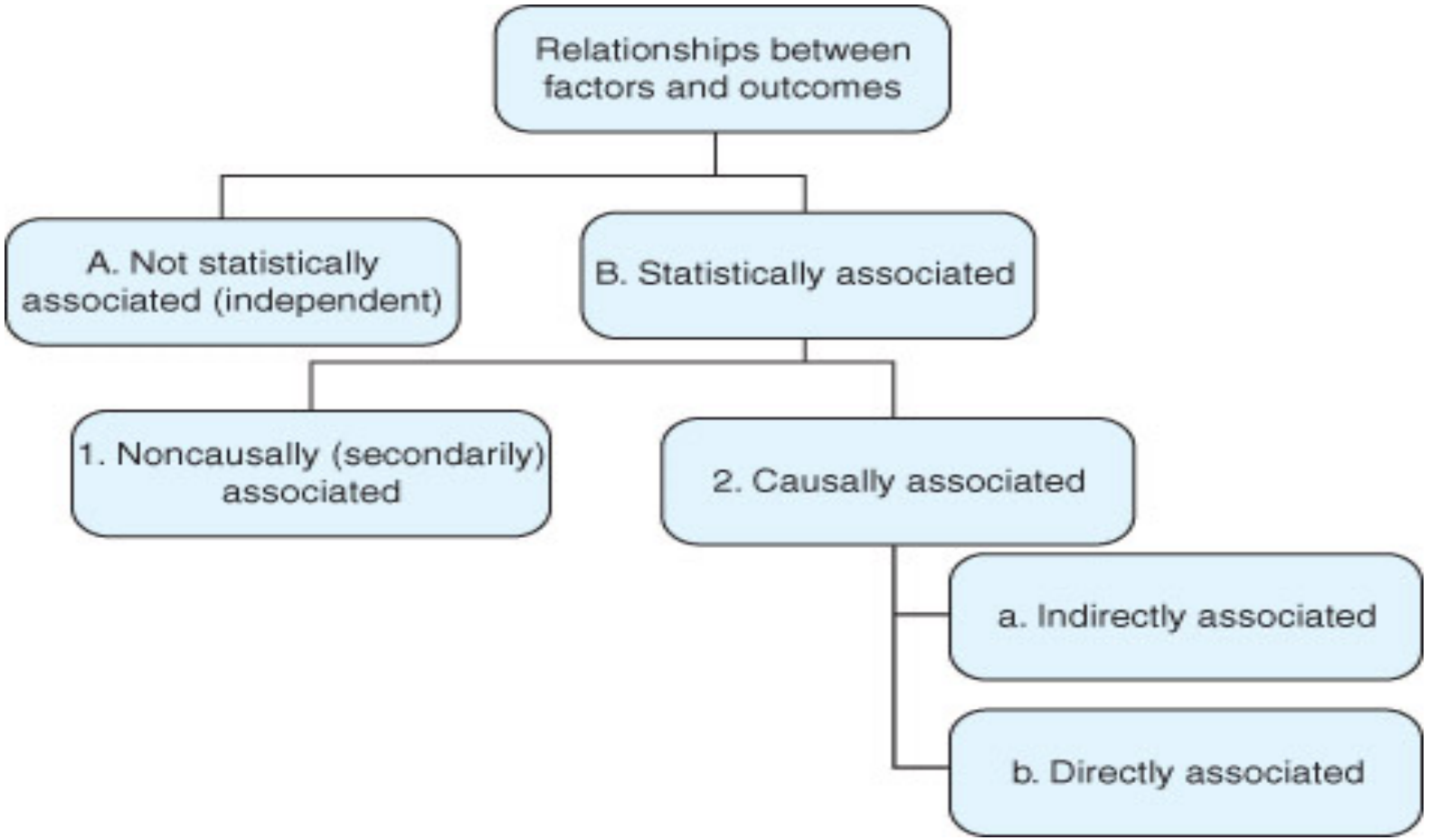
- Measure of Association
  - Quantifies a relationship between two variables, i.e. Exposure and Outcome

1. Odds Ratio (OR): Case-Control
2. Relative Risks (RR): Cohort
3. Hazard Ratio (HR): Randomized Clinical Trials

- Causation
  - One event is the result of the occurrence of the other event

Exposure (Event A)  Outcome (Event B)

Associations between exposure and outcome



Data from B MacMahon and TF Pugh, Epidemiology Principles and Methods. Boston, MA: Little, Brown and Company; 1970

Evaluating Epidemiologic Associations

- Key questions to be asked every time you evaluate an association:

1. Could the association have been observed by chance?
   i. Potentially determined through statistical tests, i.e. p-values, Confidence Intervals (CI)

2. Could the association be due to bias?
   i. Bias= Systematic errors, Ex. Sample selection or how data was analyzed

1. Gordis, Leon. (2018). *Epidemiology*. Saunders Elsevier.
2. Baker, Charlotte (2014). Introduction to Epidemiology. Virginia Tech University

Evaluating Epidemiologic Associations cont'd

3. Could other variables account for the observed relationship?
    i. Confounders, i.e. Smoking and diabetes increases the risk of Cardiovascular Disease (CVD)

4. Does this association represent a cause-and-effect relationship?
    i. Consideration for "Criteria of Causality"

1. Gordis, Leon. (2018). *Epidemiology*. Saunders Elsevier.
2. Baker, Charlotte (2014). Introduction to Epidemiology. Virginia Tech University

Measures of Association

Odds Ratio

Exposure Status	Disease Status: Yes (Cases)	Disease Status: No (Controls)
Yes	A	B
No	C	D
	A+C	B+D
Odds	A/C	B/D

Odds Ratio AD/BC

Measures of Association cont'd

- **Measures of Association- OR**

  OR>1: The odds of exposure among cases are **greater** vs controls

  OR=1: The odds of exposure is the **same** for both study groups

  OR<1: The odds of exposure among cases are **less** vs controls

  Anticoagulation with heparin did not increase the likelihood of survival to hospital discharge or medical support for respiratory adverse events among patients diagnosed with COVID-19 vs those who received the standard thromboprophylaxis [1]

  *(Adjusted OR: 0.83, 95% CI 0.67-1.03) [1]

1. Bradbury, C., McVerry, B., et al. (2021). Therapeutic Anticoagulation with Heparin in Critically Ill Patients with COVID-19. *N England J Med*. 385(9): 777-789. doi: 10.1056/NEJMoa2103417

Measures of Association cont'd

*Confidence Intervals (CI)

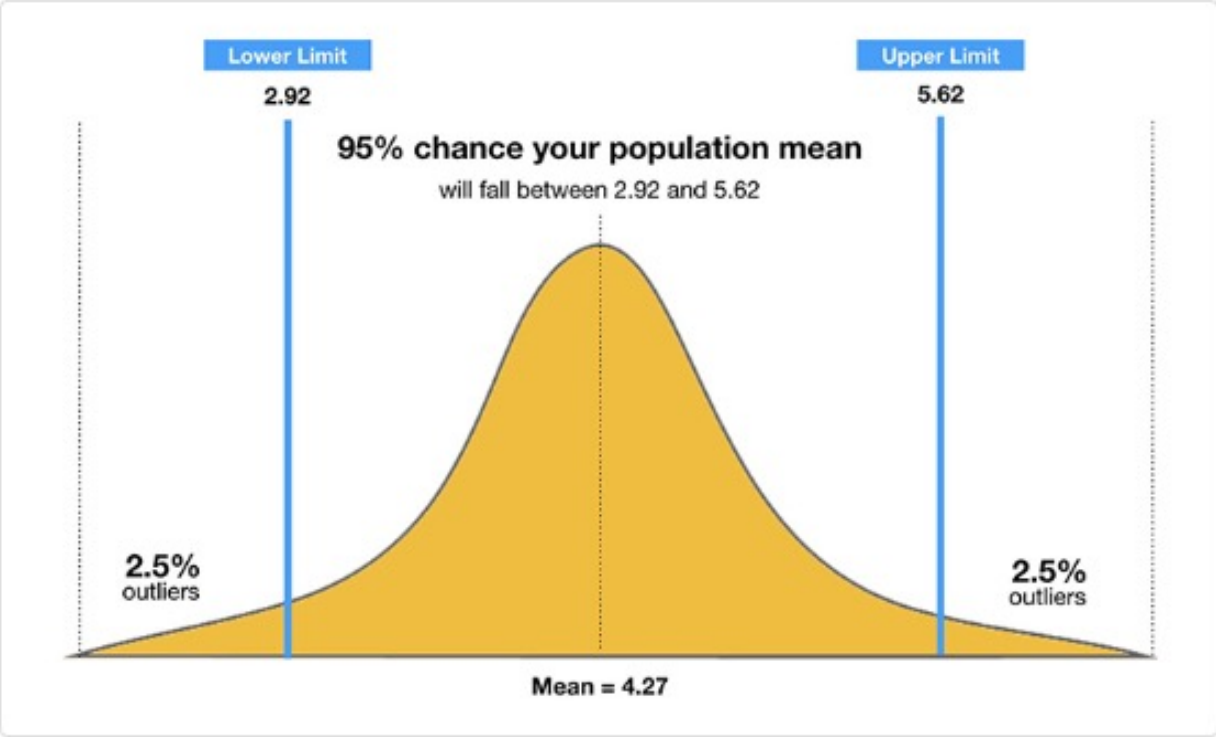
- Point estimate (i.e. OR, RR, HR) is important BUT:
- Interval of values that, with a given probability, contains the TRUE value of the population parameter
- No statistical association when the CI does include or contain 1

  Ex. (Adjusted OR: 0.83, 95% CI 0.67-1.03)[1]

1. Bradbury, C., McVerry, B., et al. (2021). Therapeutic Anticoagulation with Heparin in Critically Ill Patients with COVID-19. *N England J Med*. 385(9): 777-789. doi: 10.1056/NEJMoa2103417

Measures of Association cont'd

Confidence Intervals (CI)



1. Gordis, Leon. (2018). *Epidemiology*. Saunders Elsevier.

Measures of Association cont'd

Relative Risk

	Disease Status			Incidence
Exposure Status	Yes	No	Totals	Total
Yes	A	B	A+B	A/(A+B)
No	C	D	C+D	C/(C+D)
	A + C	B + D	N	

Relative Risk [A/A+B]/[C/C+D]

Measures of Association cont'd

- **Measures of Association- RR**

  RR>1: The risk in exposed group is **greater** than the risk in non-exposed group

  RR=1: The risk in exposed group is **=** to the risk in non-exposed group

  RR<1: The risk in exposed group is **less** than the risk in non-exposed group

  - Shift work and insufficient sleep increased risk of coronary heart disease [1]

    (RR: 1.23, 95% CI 1.15-1.31)

1. Kecklund, G., Axelsson, J. (2016). Health consequences of shift work and insufficient sleep. *BMJ*. 355. doi.org/10.1136/bmj.i5210

Measures of Association cont'd

Hazard Ratio (HR)

Time (t)

$$\text{Hazard} = \frac{HR_{Exposed}(t)}{HR_{Unexposed}(t)}$$

Measures of Association cont'd

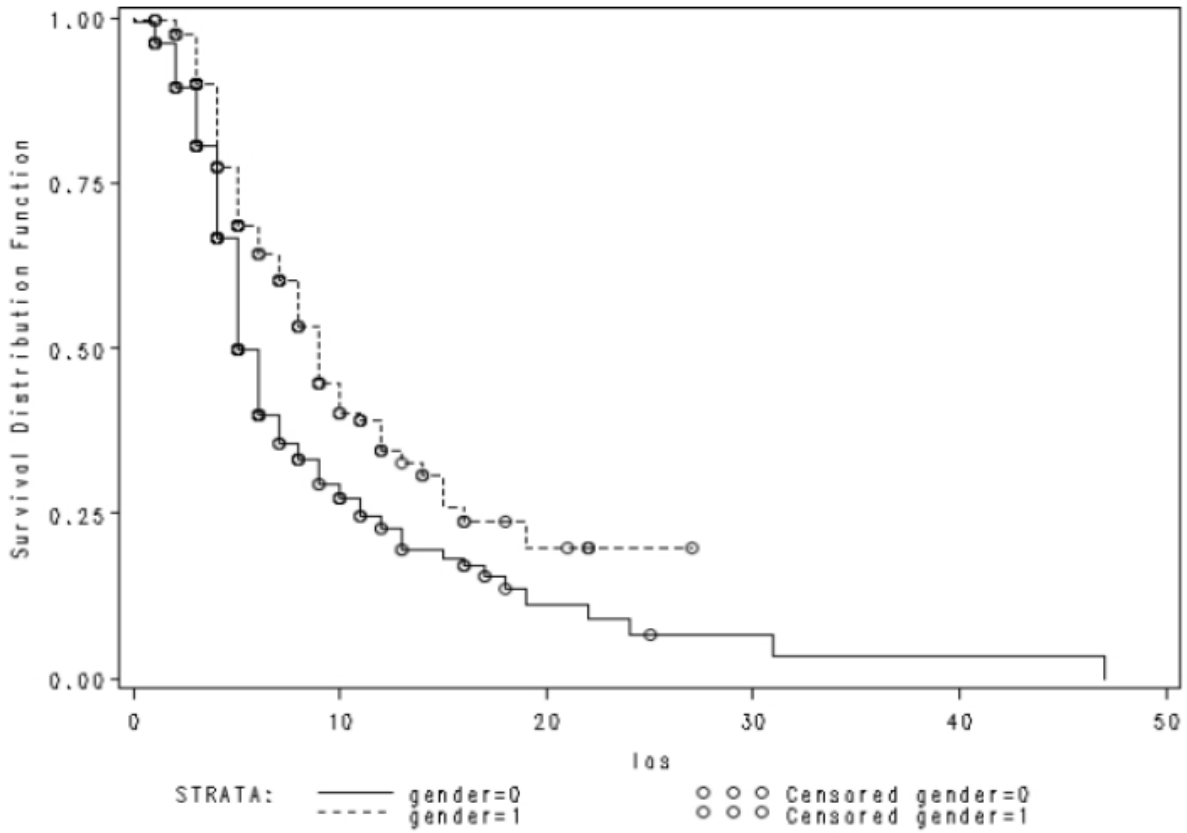
HR can be calculated using:

1. Cox Proportional Hazards Model
2. Kaplan Meier Curve

Measures of Association cont'd

Kaplan Meier Curve: Acute Myocardial Infarction (MI)

Birth Sex:
0= Male
1= Female



1. Millett, E. et al. (2018). Sex Differences in Risk Factors for Myocardial Infarction: Cohort Study of UK Biobank Participants. *BMJ*. 363. doi: https://doi.org/10.1136/bmj.k4247

Measures of Association cont'd

- **Measures of Association- HR**

  HR>1: The hazard in exposed group is greater than the non-exposed group

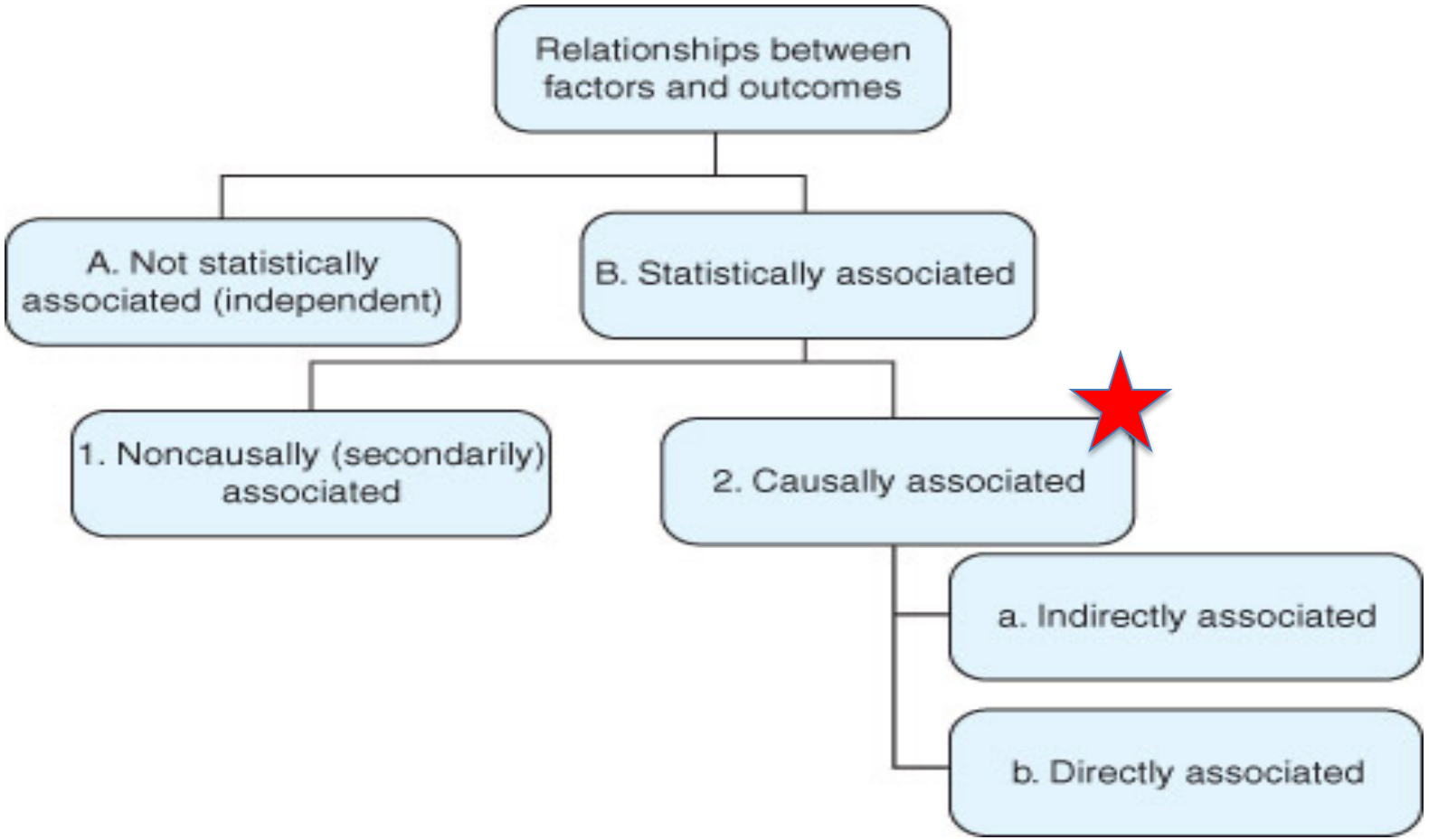
  HR=1: The hazard in exposed group is the same in non-exposed group

  HR<1: The hazard in exposed group is less than the non-exposed group

  - Cardiovascular Rx reduces risk of major cardiovascular events in patients w/ Type II diabetes and previous myocardial infarction[1] (HR: 0.84, 95% CI 0.72-0.99)

1. Furtado, R., Bonaca, M., et al. (2019). Dapagliflozin and Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus and Previous Myocardial Infarction. *Circulation*. 139(22): 2516-2527. doi: 10.1161/CIRCULATIONAHA.119.039996.

Associations between exposure and outcome



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Evaluating Criteria for Causation

Five key questions to determine causation, *Hill's Criteria*:

1. Biological Plausibility
    i. Is there a reasonable pathway to link exposure to outcome

2. Consistency
    i. Can the same results occur if repeated in a different time, place, person?

1. Gordis, Leon. (2018). *Epidemiology*. Saunders Elsevier.

Evaluating Criteria for Causation cont'd

3. Temporality
    i. Does the exposure occur before the outcome?

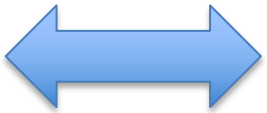
4. Strength
    i. Is there strength in the relationship between the exposure and outcome, with or without a dose-response relationship?

5. Specificity
    i. Is the outcome unique or specific to the exposure?

1. Gordis, Leon. (2018). *Epidemiology*. Saunders Elsevier.

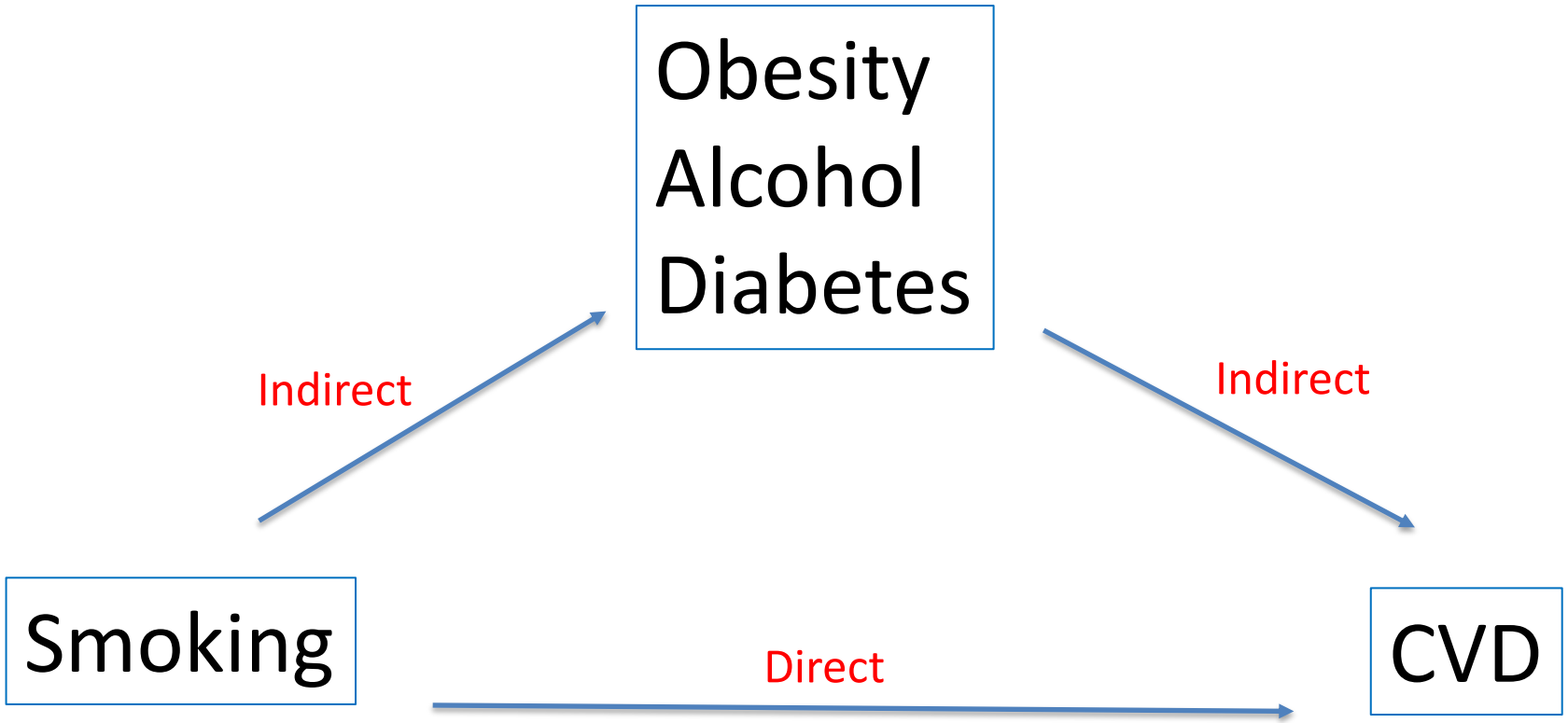
Causation

- "….requirement that one or more factors be present for disease to develop.."[1]
  1. Direct: No intervening causes or factors that result in outcome
  2. Indirect: Intervening causes or factors that still result in outcome

- Mutiple Causality  Multifactorial Etiology

1. Gordis, Leon. (2018). *Epidemiology*. Saunders Elsevier.

Causation cont'd



1. Gordis, Leon. (2018). *Epidemiology*. Saunders Elsevier.
2. Leary, P. (2016). Causality, Correlation, and Cardiac Disease: Does Smoking cause Cardiac Hypertrophy and Diastolic Dysfunction. *Circulation: Cardiovascular Imaging*. 9(9). doi.org/10.1161/CIRCIMAGING.116.005441

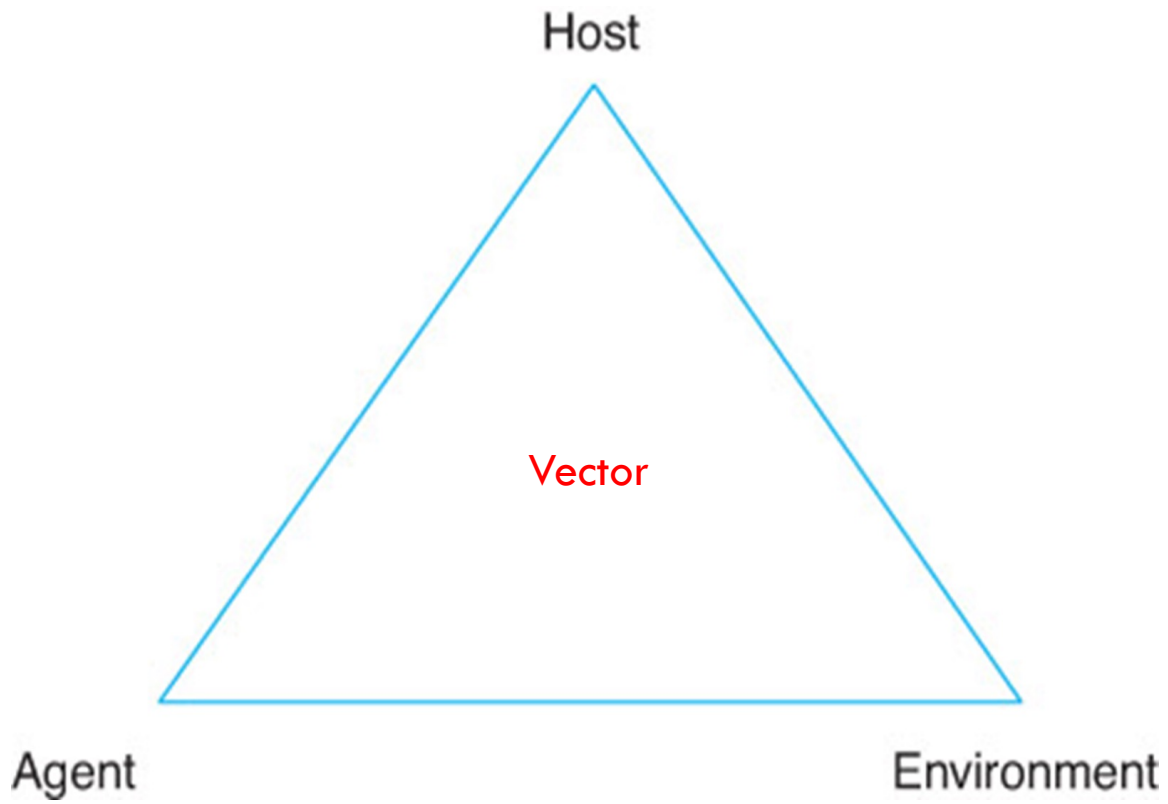
Causation cont'd

- Models of Multiple Causality
  - Epidemiologic Triangle
  - Web of Causation
  - Wheel Model
  - Pie Model

- Causal Models help to interpret Epidemiological data

Causation cont'd

- Epidemiologic Triangle
  - Intersection of the Host, the Agent, the Environment, and **Vector
  - Ex. Malaria
  1. Host- Person
  2. Agent- *Plasmodium falciparum*
  3. Environment- Hot, Humid, Tropical Climate
  4. Vector- Mosquito



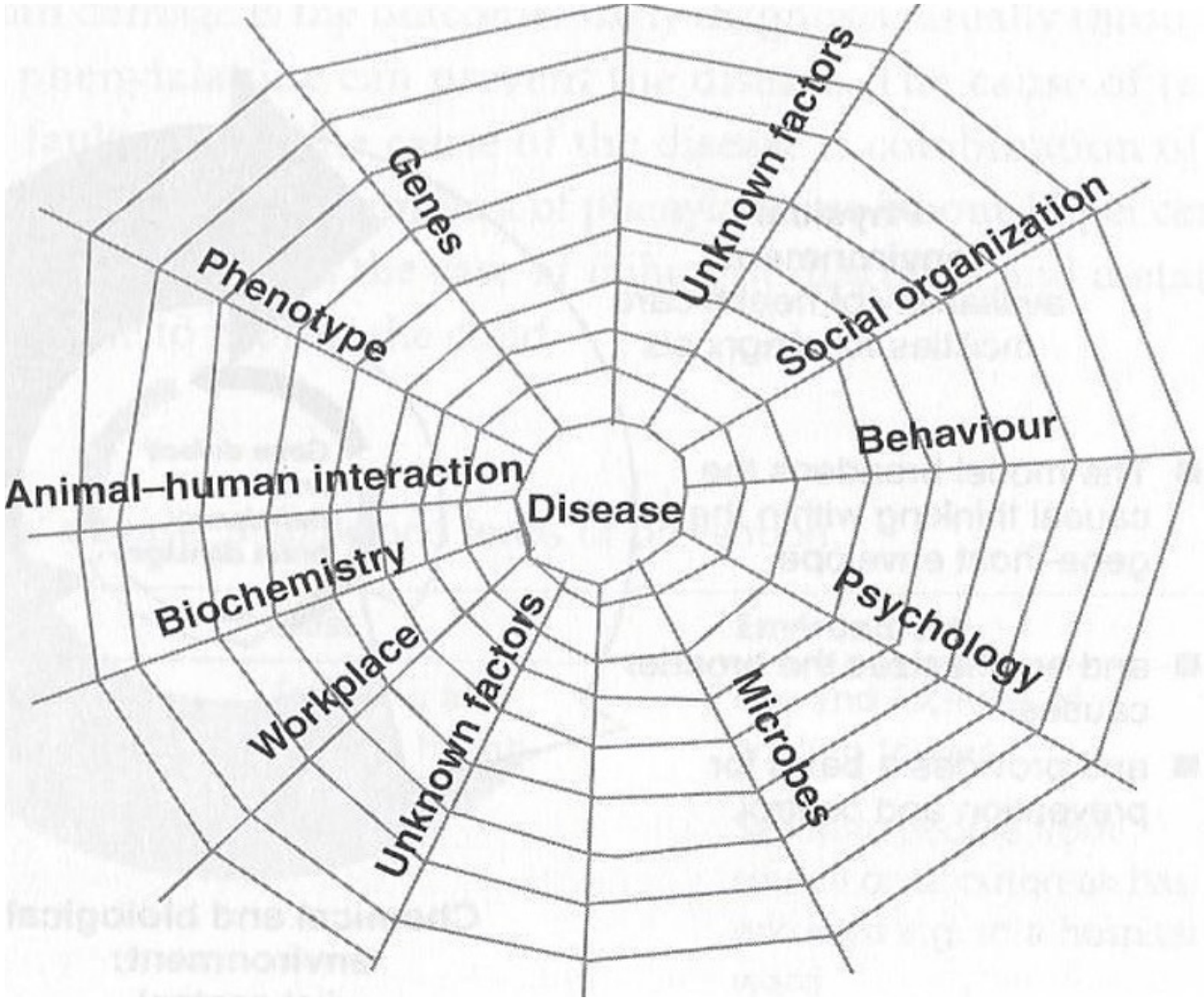
1. Gordis, Leon. (2018). *Epidemiology*. Saunders Elsevier.

Causation cont'd

- Web of Causation
  1. No single cause
  2. Causes of disease are interacting
  3. Causality may be two way

Ex. Disease→ CVD

- Genetics, Behavior, Stress, etc.



1. Gordis, Leon. (2018). *Epidemiology*. Saunders Elsevier.

Summary

ASSOCIATION ≠ CAUSATION

Summary cont'd

Estimation of Study

- Measure of Association-Quantification of relationship between two variables

Ex. Statistical association between smoking and CVD

- Causation-One event is the result of the occurrence of the other event

Ex. Smoking causes CVD[1]

1. Leary, P. (2016). Causality, Correlation, and Cardiac Disease: Does Smoking cause Cardiac Hypertrophy and Diastolic Dysfunction. *Circulation: Cardiovascular Imaging*. 9(9). doi.org/10.1161/CIRCIMAGING.116.005441