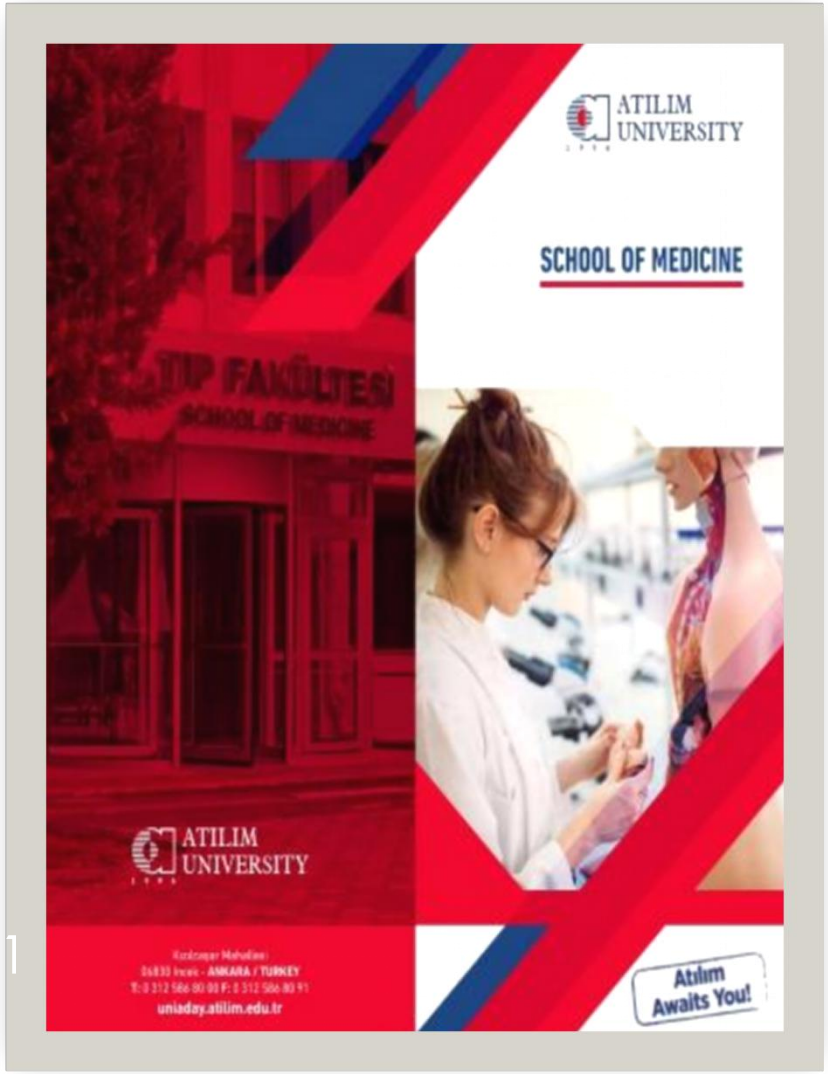

Casualty in Medicine: Meaning and Critical Function

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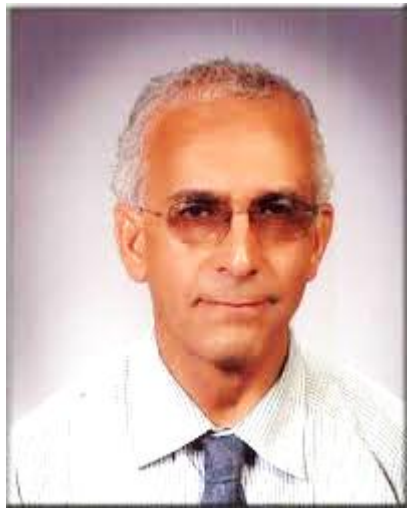


The relating of causes to the effects they produce. Most of epidemiology concerns causality and several types of causes can be distinguished. It must be emphasised, however, that epidemiological evidence by itself is insufficient to establish causality, although it can provide powerful circumstantial evidence.

Phase 1 lecture, 2021 - 2022 academic year, spring semester

12th Oct. 2021, Ankara - TURKIYE

www.ahmetsaltik.net

What is Association?

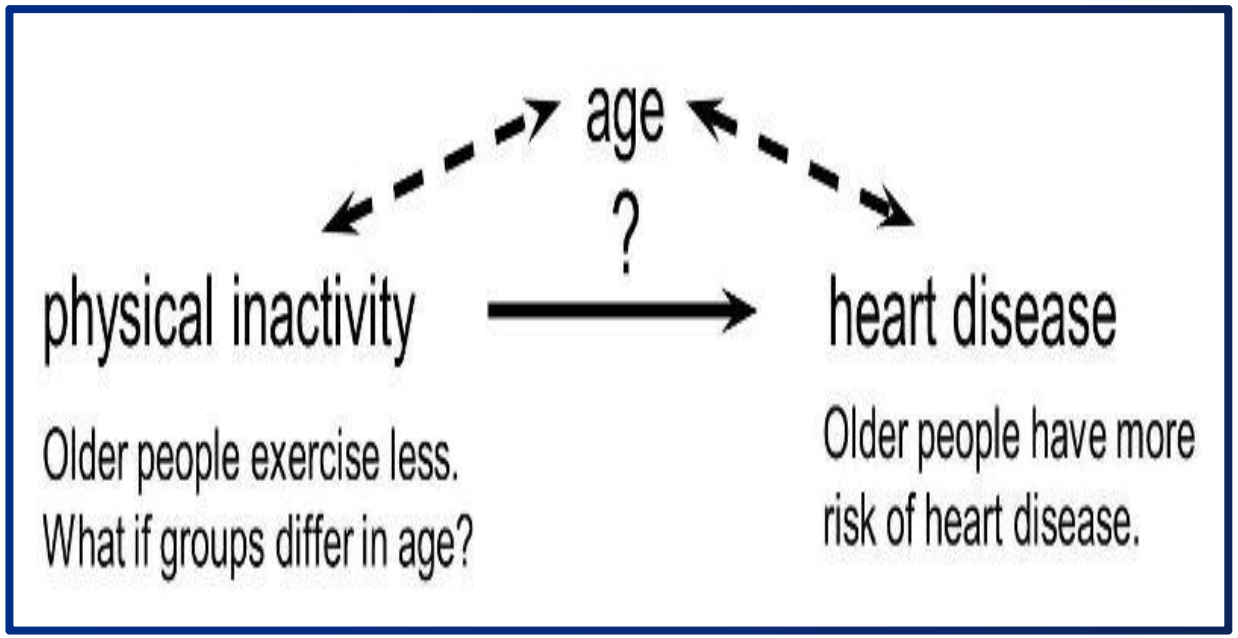
- *Statistical dependence between two or more events, characteristics, or other variables.*
- An **association** may be fortuitous *(by chace)* or may be produced by various other circumstances; the presence of an association does not necessarily imply a ***causal relationship***.

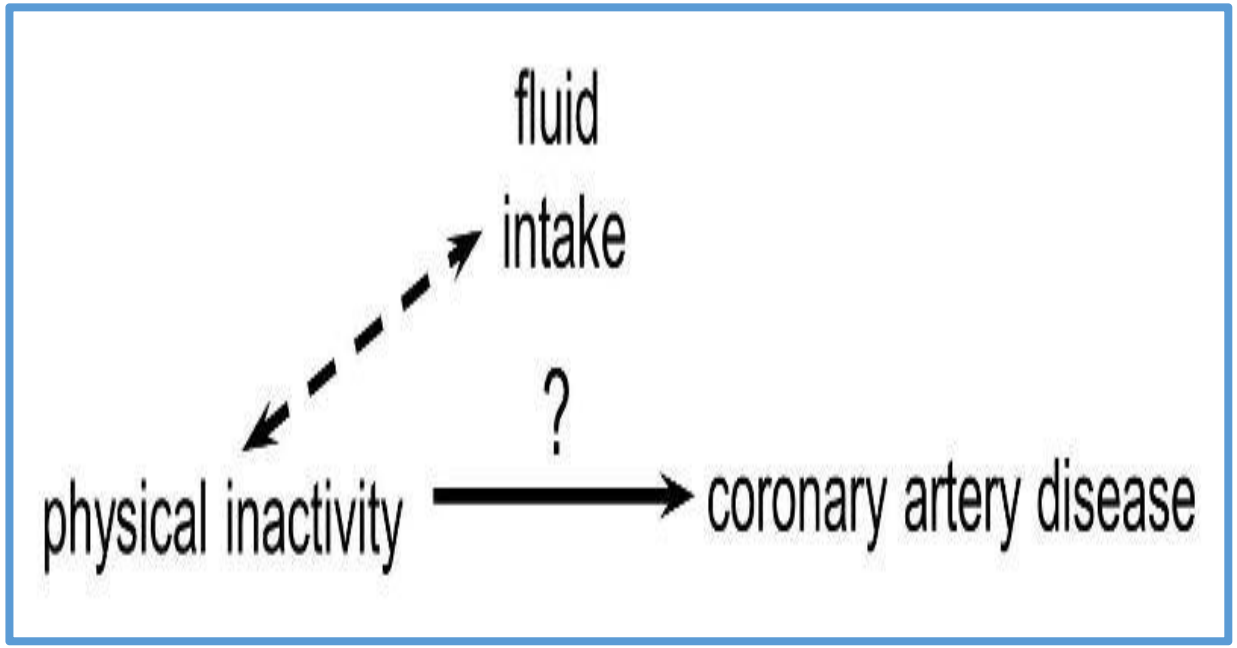
Causality is the science of cause and effect

International Epidemiological Association

What is Confounding?

- ***Confounding variable, confounder***
  A variable that can cause or prevent the outcome of interest, is not an intermediate variable, and is ***associated*** with the factor under investigation.
- A **confounding variable** may be due to chance or bias. Unless it is possible to adjust for confounding variables, their effects cannot be distinguished from those of factor(s) being studied.



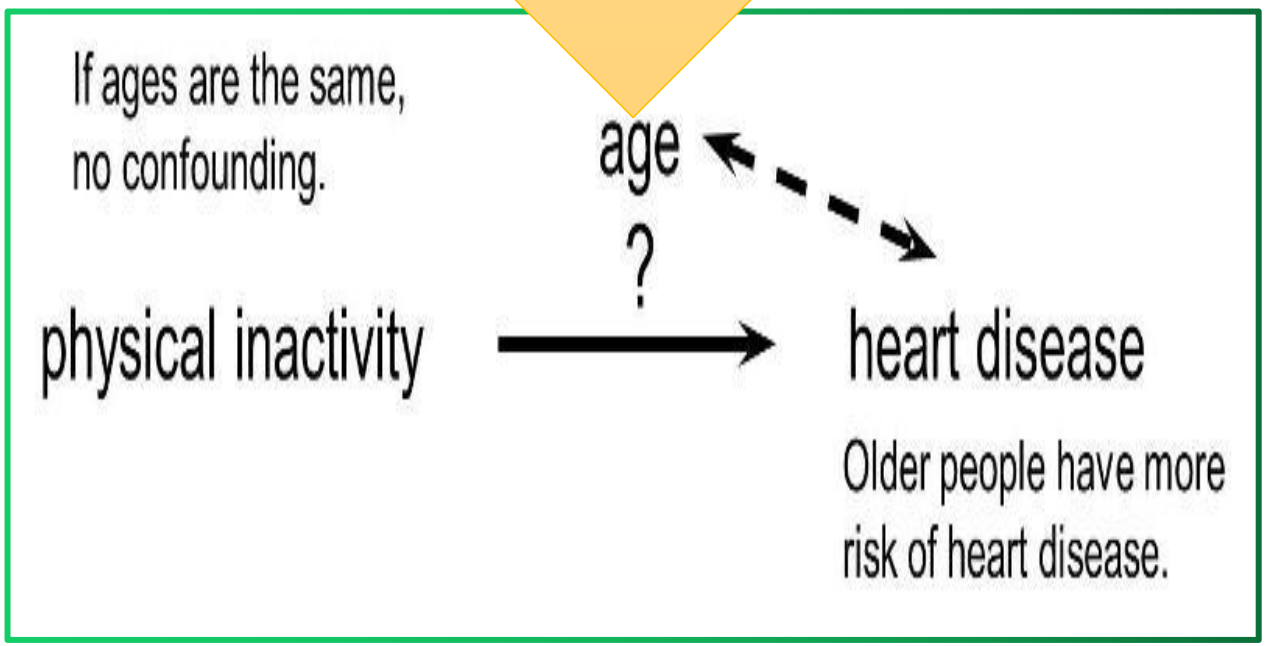


https://sphweb.bumc.bu.edu/otlt/mph-modules/bs/bs704-ep713_confounding-em/BS704-EP713_Confounding-EM2.html

What is Confounding?

- **Confounding** is a distortion (inaccuracy) in the estimated measure of association that occurs when the primary exposure of interest is mixed up with some other factor that is associated with the outcome.
- *In the diagram right, the primary goal is to ascertain the strength of association between physical inactivity and heart disease.*
- Age is a **confounding factor** because it is associated with the exposure *(meaning that older people are more likely to be inactive)*, and it is also associated with the outcome *(because older people are at greater risk of developing heart disease)*.

Most health problems have many determinants (risk factors), so it is not surprising that there is a lot of potential for confounding. While this can represent a barrier to testing a particular hypothesis, it is also an opportunity to dissect the many determinants and to define their relative importance.



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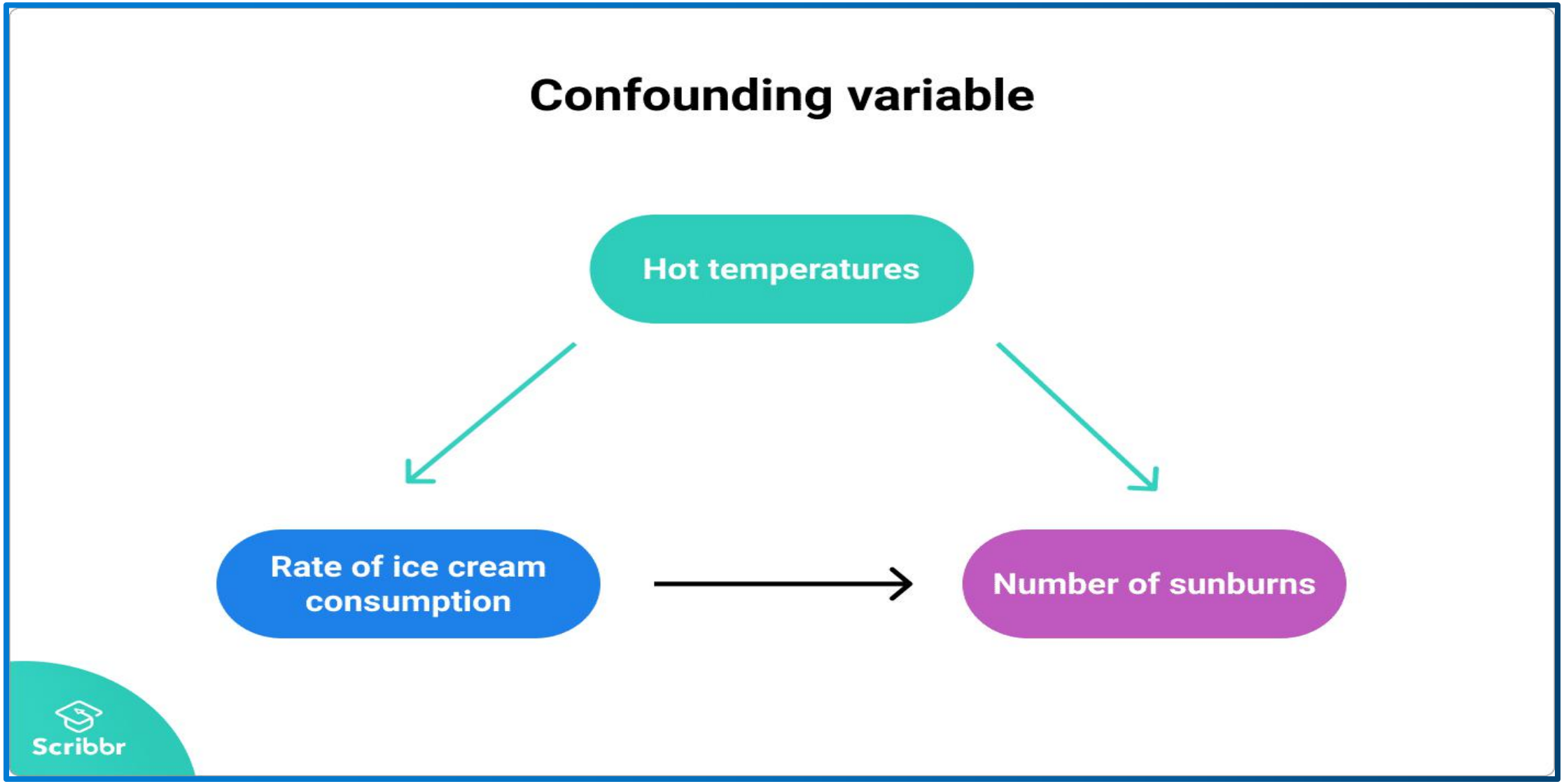
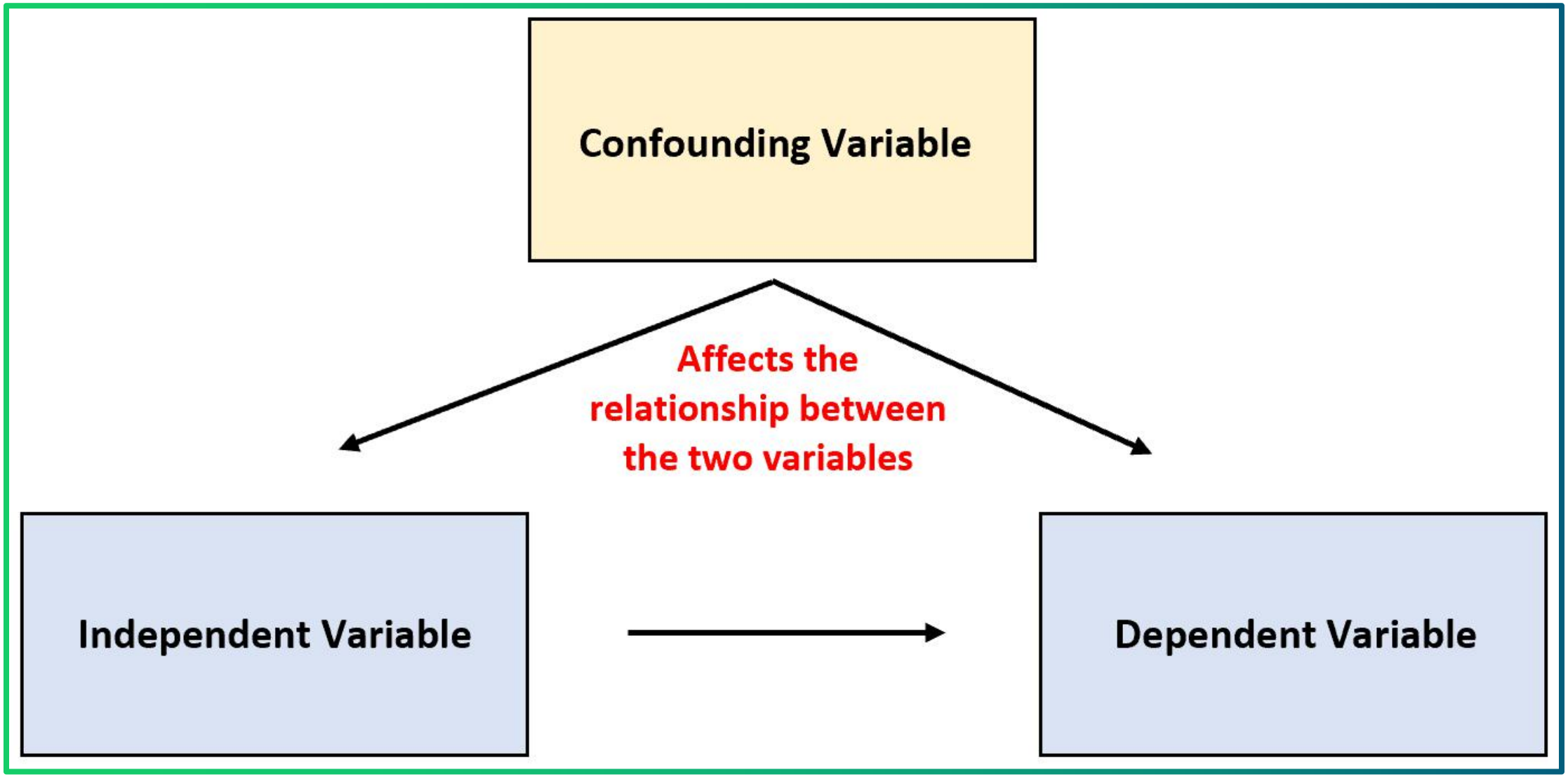
What is Confounding?



What is Confounding?



Causality : *A major topic in medicine*

- Causality has always been a major topic in medicine.
- *It is important to know the cause of disease not only to enable the best possible treatment, but also to develop the best possible diagnostic tests.*
- Everyone knows that it is dangerous to treat fever with antibiotics without knowing its cause.
- *But, on the contrary, it is reasonable to withhold treatment because we do not know the cause?*
- That unfortunately, is often the dilemma in many medical disciplines.

https://doi.org/10.1016/j.crvi.2019.03.001

Causality : *Complex situations*

- Most everyone would agree that looking for the cause of an event is a natural thing to do.
- ***This is particularly so in medicine.***
- Sometimes the response is simple, unequivocal, for instance when there is an obvious genetic or environmental cause.
- Elsewhere, in more **complex situations**, it is less straightforward.

https://doi.org/10.1016/j.crvi.2019.03.001

Is an event causal??

- Emphasis is often placed on chronology
  -the striking effect of a sequence of events-
  despite the lack of any link to causality.
- *This attitude often leads to errors, especially if the public is poorly informed, the side effects of vaccinations being a caricatured example.*
- In other situations, no precise cause can be found.

https://doi.org/10.1016/j.crvi.2019.03.001

Finding precise cause is not so easy

- In other situations, no **precise cause** can be found.
- *Indeed, many diseases have a multi-factorial origin associating factors of genetic, epigenetic, and environmental predisposition.*
- The disease is caused, or its progress favored, by a group of factors that, taken individually, have little or no effect.
- Such complex situations are difficult to analyze despite the progress made possible by recent advances in genetics and biology, epidemiology, and other disciplines.

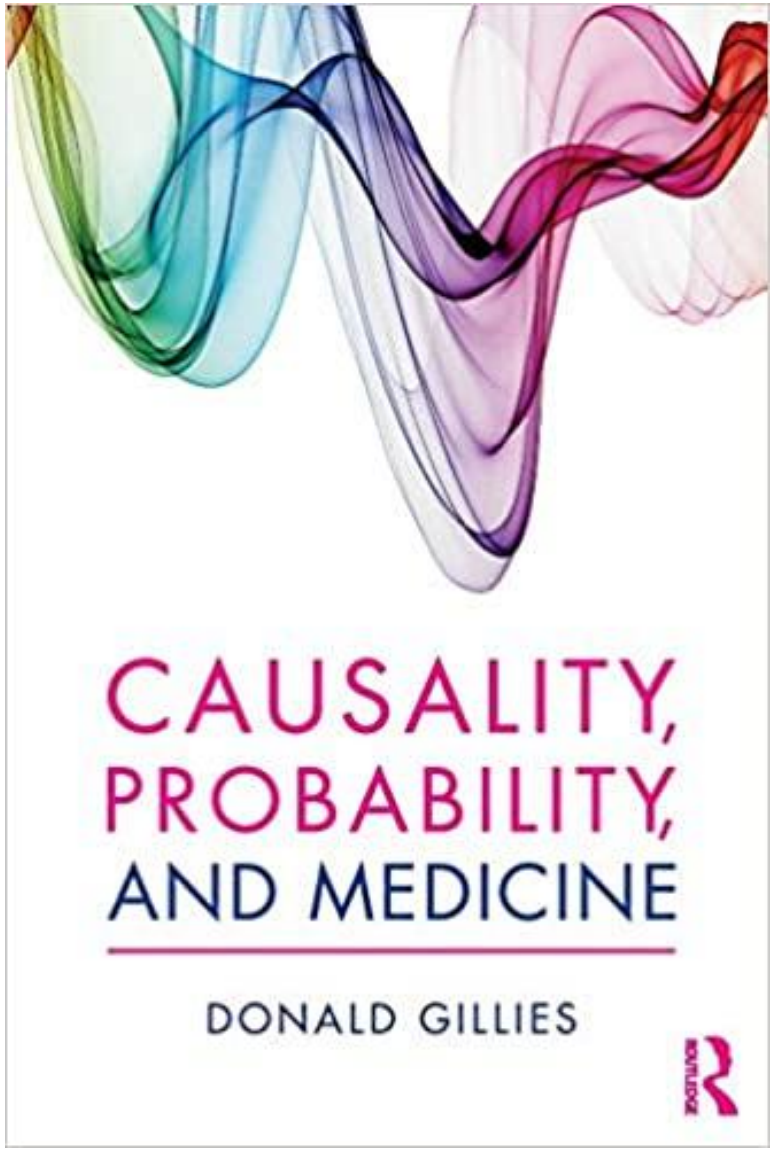
https://doi.org/10.1016/j.crvi.2019.03.001

Principles of Causality

- ***Hill's Criteria of Causation*** **outlines:**
- **Minimal conditions needed to establish a causal relationship between two items**
- **Criteria were originally presented by Austin Bradford Hill (1897-1991), a British medical statistician as a way of determining the causal link between a specific factor (e.g., cigarette smoking) and a disease (such as emphysema or lung cancer)**
- ***Hill's Criteria*** **form the basis of modern epidemiological research**
- **attempts to establish scientifically valid causal connections between potential disease agents and the many diseases that afflict humankind.**

Apparently simple cases

- In certain cases, the situation is apparently very simple, the cause is obvious.
- *Infection is a good example, when the responsible pathogenic agent is known.*
- This is also the case for monogenic diseases when the genetic mutation or anomaly is recognized.
- *However, even in these cases, the situation is not always as simple as it would appear.*



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Causality in contagious infections

- For instance, in contagious infections, we know that not everyone will get the disease during an epidemic, an observation probably related to genetic factors.
- *Nevertheless, the infectious agent is still the cause of the disease, even though only a certain number of individuals with a mutation inducing a particular immune deficiency become ill, generally severely.*
- But this remains exceptional; most carriers of the mutation in question are not susceptible to infectious diseases other than the one associated with the mutation.

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Causality for monogenic diseases

- For monogenic diseases, the question is one of penetrance.
- *In certain configurations all individuals carrying the mutation present the disease, while in others, expression is highly variable from one individual to another, both in terms of severity and age of onset.*
- There are even cases where the disease does not develop despite the presence of the mutation.
- *Many often poorly understood factors can affect penetrance.*
- Epistasis, other genes interacting with the disease-causing mutated gene, may be involved.
- In other situations, environmental factors modulate disease expression.

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Causality in multifactorial diseases

- Very often, diseases are ***multifactorial***.
- *For the simplest situations, this can correspond to the combined effects of several identified factors, somewhat like an airplane accident where many causes, sometimes five or six, have an additive effect:*
- Each cause taken individually, or even associated with several others, is insufficient to trigger the accident.

https://doi.org/10.1016/j.crvi.2019.03.001

Causality in multifactorial diseases

✓*This type of situation -**the additive effect of external factors**- is well known in medicine.*

✓For example, in **coeliac disease**, ingestion of gluten is a prerequisite for disease expression.

✓*But, of course, symptoms do not develop in everyone who eats **gluten**-containing food.*

✓In fact, for most patients, the situation is much more complex:

✓*Poorly understood interactions occur between genetic and environmental factors.*

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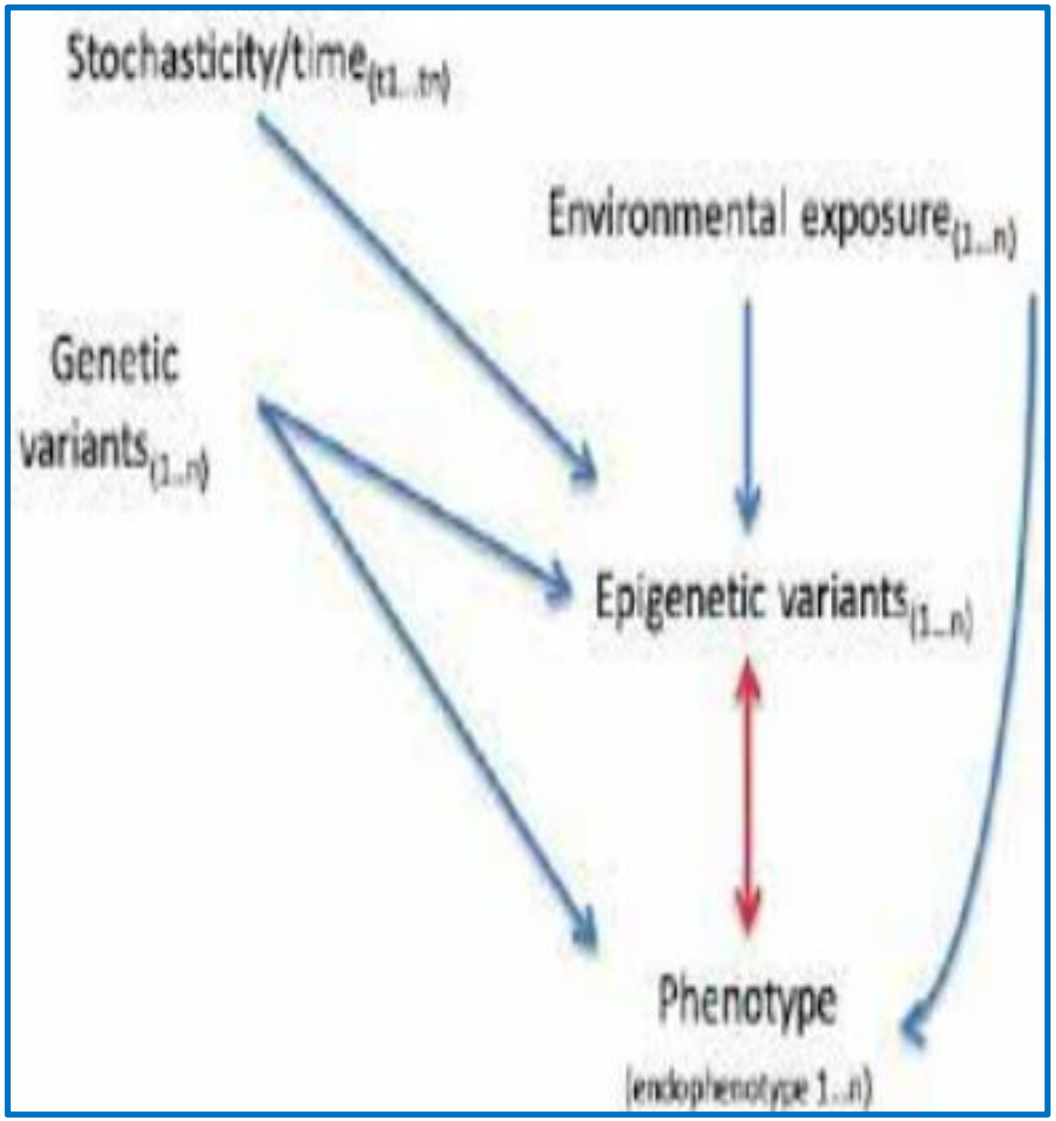
Causality in genetic diseases

- Genetic factors can be expressed in several ways.
- **Predisposition** -*let us hazard the term cause in certain cases*- can be inscribed in the inherited parental genome.
- This is ***hereditary disease***, caused by one or many genes.
- But it must be noted that in the multiple-gene configuration, hereditary familial disease does not occur if the **genetic factor** is expressed insufficiently.
- The role of heredity is thus very limited, but nevertheless very significant.

https://doi.org/10.1016/j.crvi.2019.03.001

Causality in genetic diseases

- The greatest problem we are facing today is to determine which genes and mechanisms support the genetic control of diseases with a hereditary component.
- *The emergence of modern genomic techniques generated great hope.*
- Considerable effort was devoted to the identification of predisposing genes in large cohorts of several thousands of patients using highly sophisticated methods such as ***genome-wide association studies (GWAS)***.



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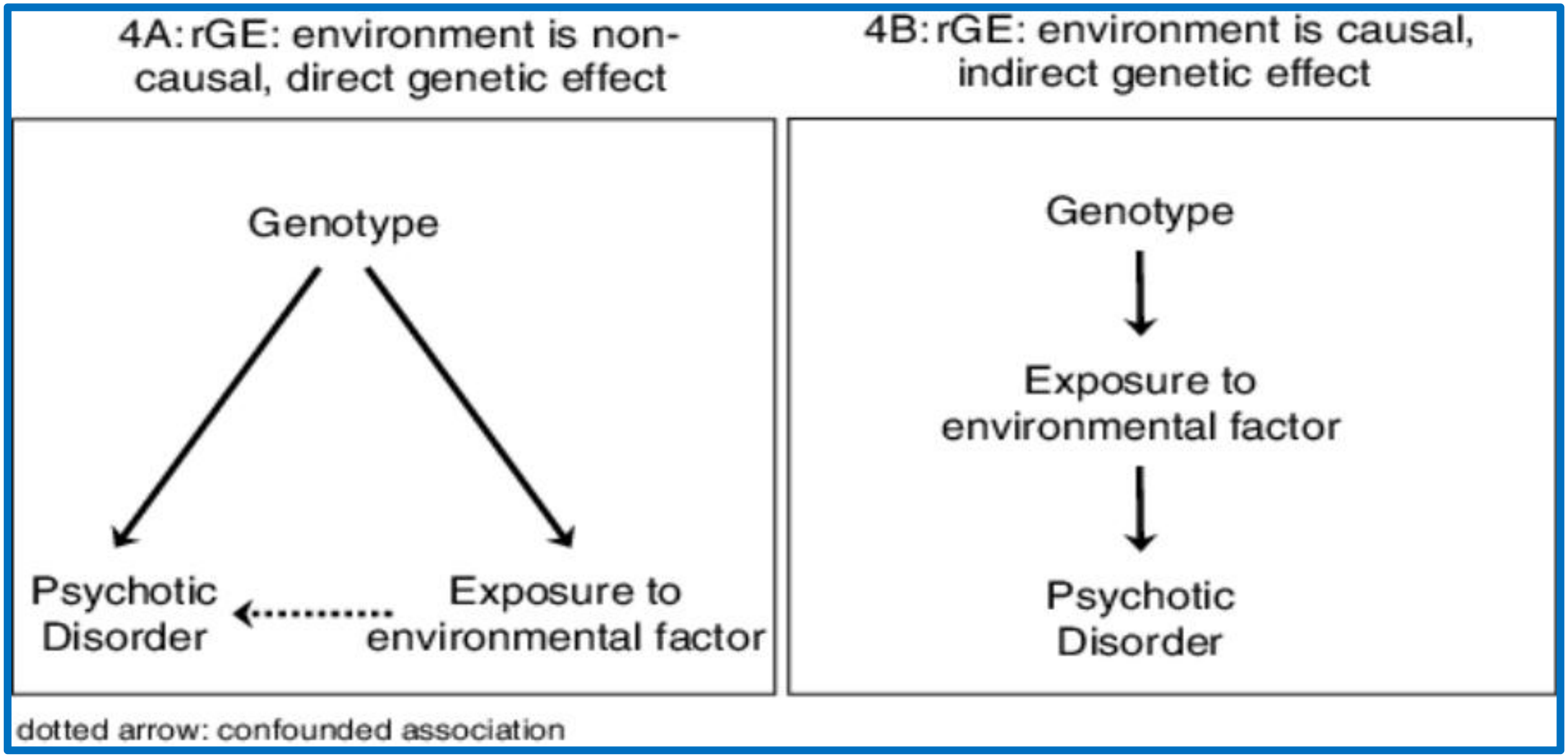
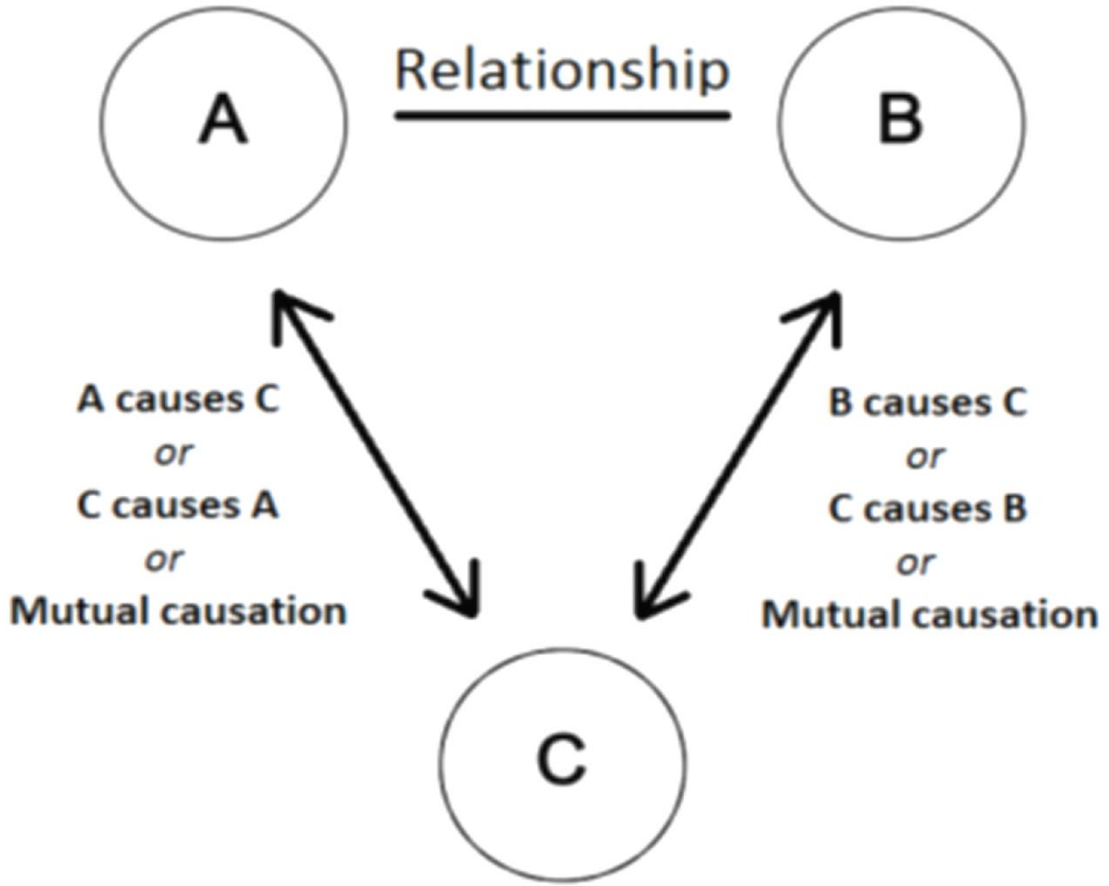
Causality in genetic diseases



Causality & Environment

- ✓The viral infection may have occurred long before the onset of overt disease, explaining why its stigmata would be so difficult to identify.
- ✓*This causal infection might also be non-specific, i.e. widespread in the general population.*
- ✓The pathogenic process would thus involve a specific individual response to a potentially common viral infection.



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Causality & Environment

- *The effect of the environment is of course crucial, but also very complex.*
- For the ecologist, the environment refers essentially to the physical, chemical or climatic context in which an individual lives.
- For the geneticist, many other factors are involved, including the group of factors that lead to an interesting fact:
- Strong heredity in certain polygenic diseases is associated with a rate of concordance between monozygotic twins that rarely exceeds 40-50% despite the fact that monozygotic twins live in a very similar environment, at least during childhood.

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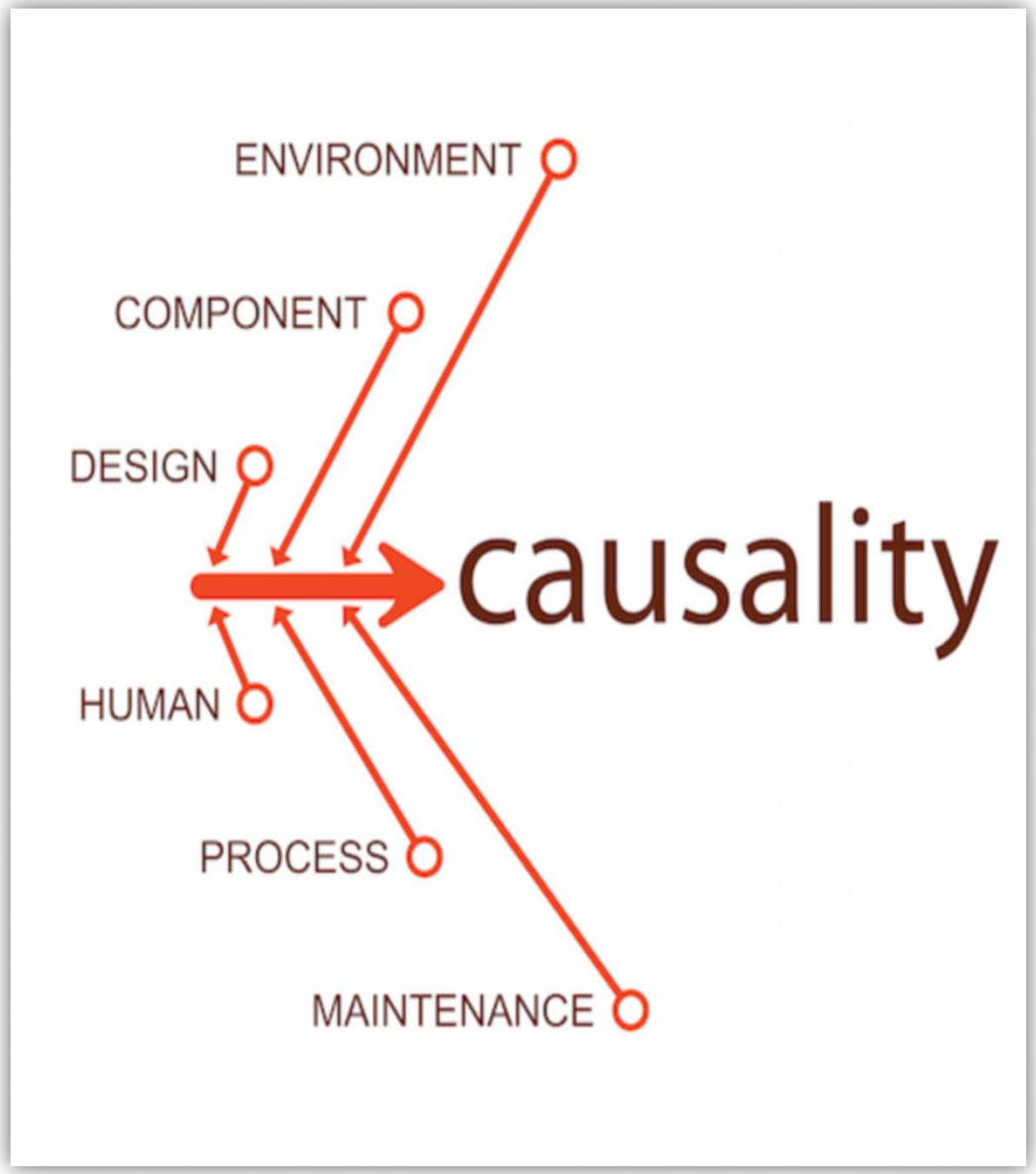
Causality & Environment

- This results from personal factors including individual behavior, in particular dietary habits and use of addictive substances such as alcohol and tobacco.
- *These factors also include interpersonal relations with other individuals, the educational context, and more generally the cultural context.*



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A prototype disease : Type 1 DM

- Here, we propose to examine this complexity, illustrating our discussion with the particularly well-documented search for the cause of a prototype disease, ***insulin-dependent diabetes mellitus*** (Type 1 DM).

- *The role of environment in the genesis of* **insulin-dependent diabetes** *has been the object of extensive study. Over the last 20 years, a large body of work has been devoted to the search for a viral cause. Particular attention has been given to Coxsackie-type enterovirus.*

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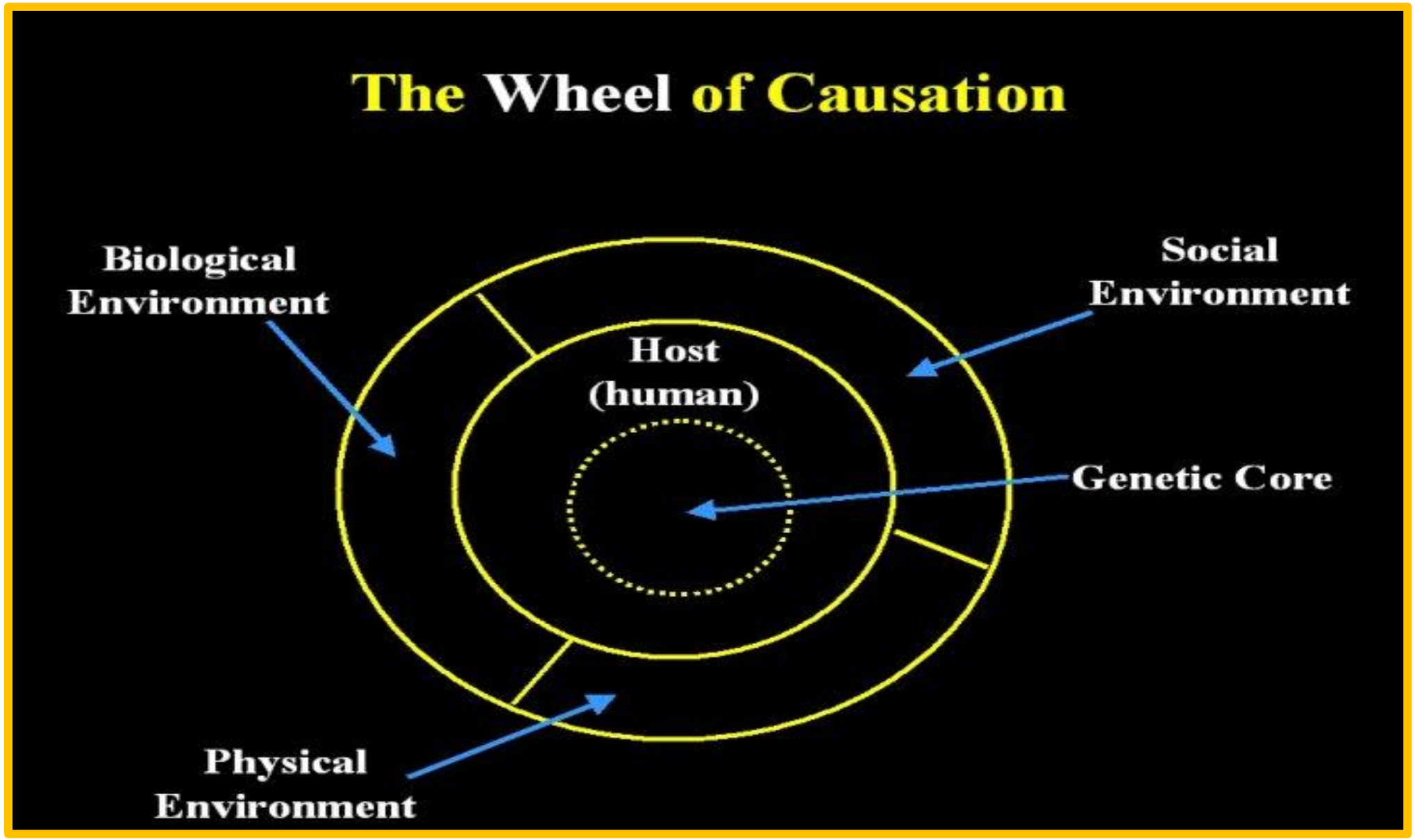
Causality & Environment



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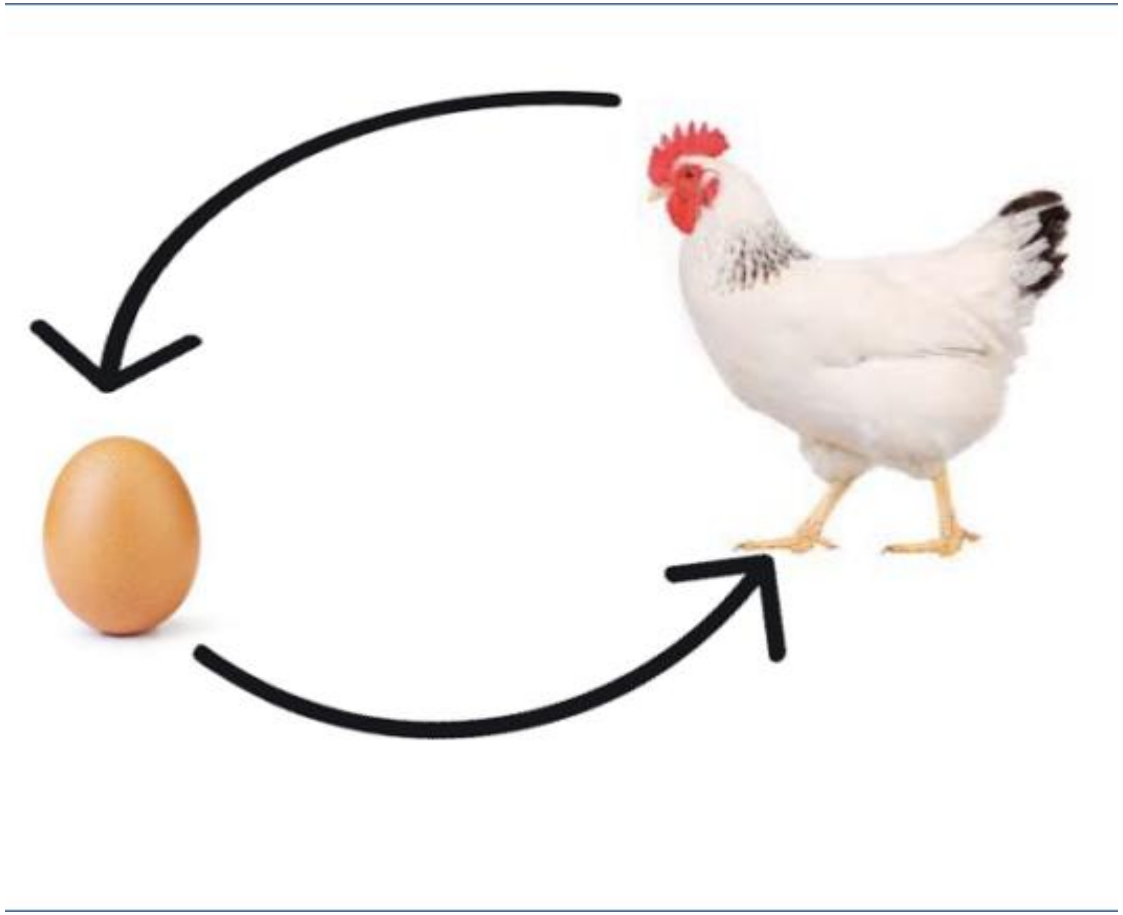
Causality & Environment

- Certain epidemiological, serological or even molecular arguments have been brought together, but are not particularly convincing.
- *The evidence is also uncertain for other autoimmune diseases such as multiple sclerosis, despite the fact that the pathogenic process begins very much like a viral infection that triggers autoimmune disease secondarily.*



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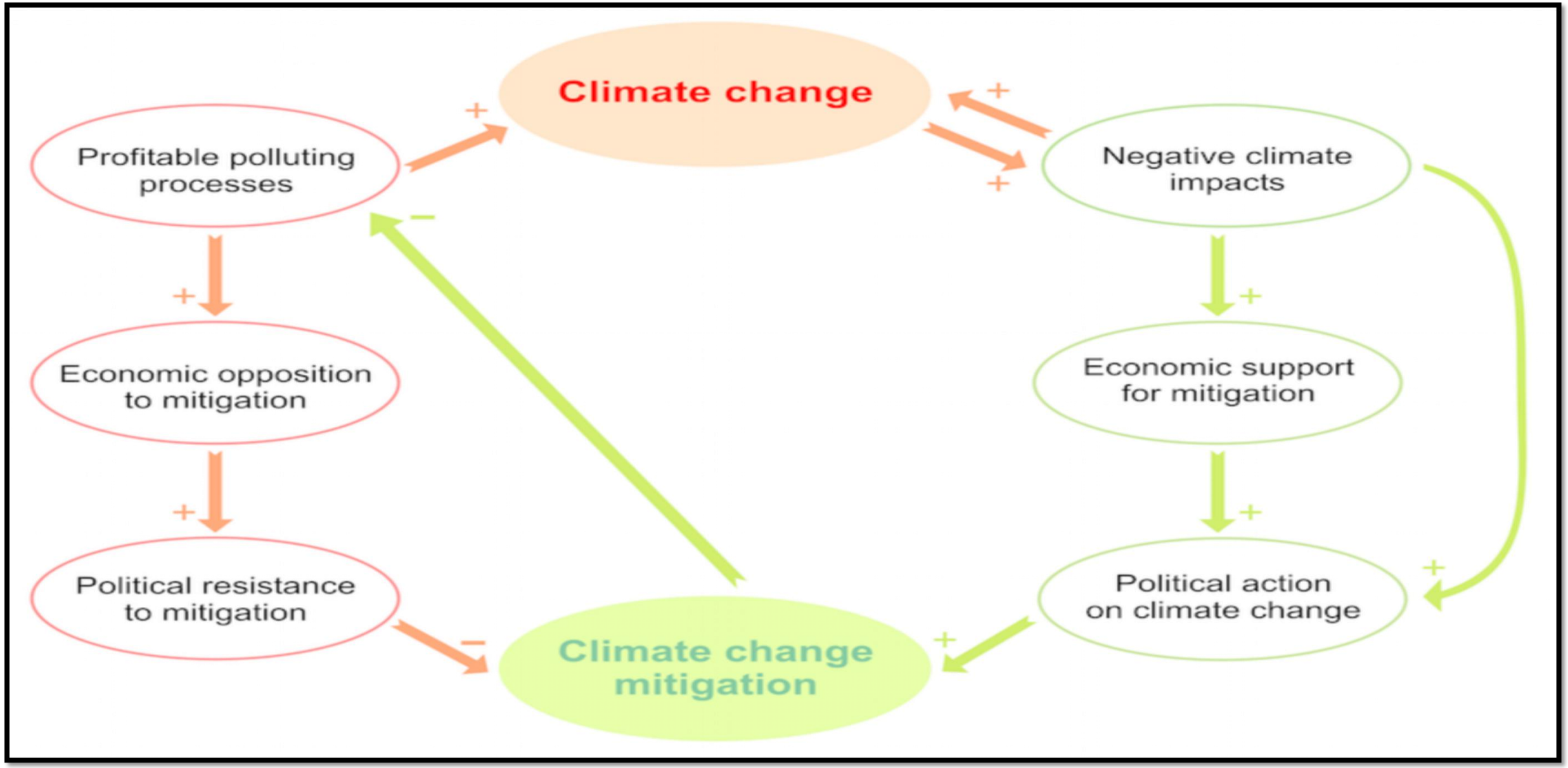
Causality & Environment

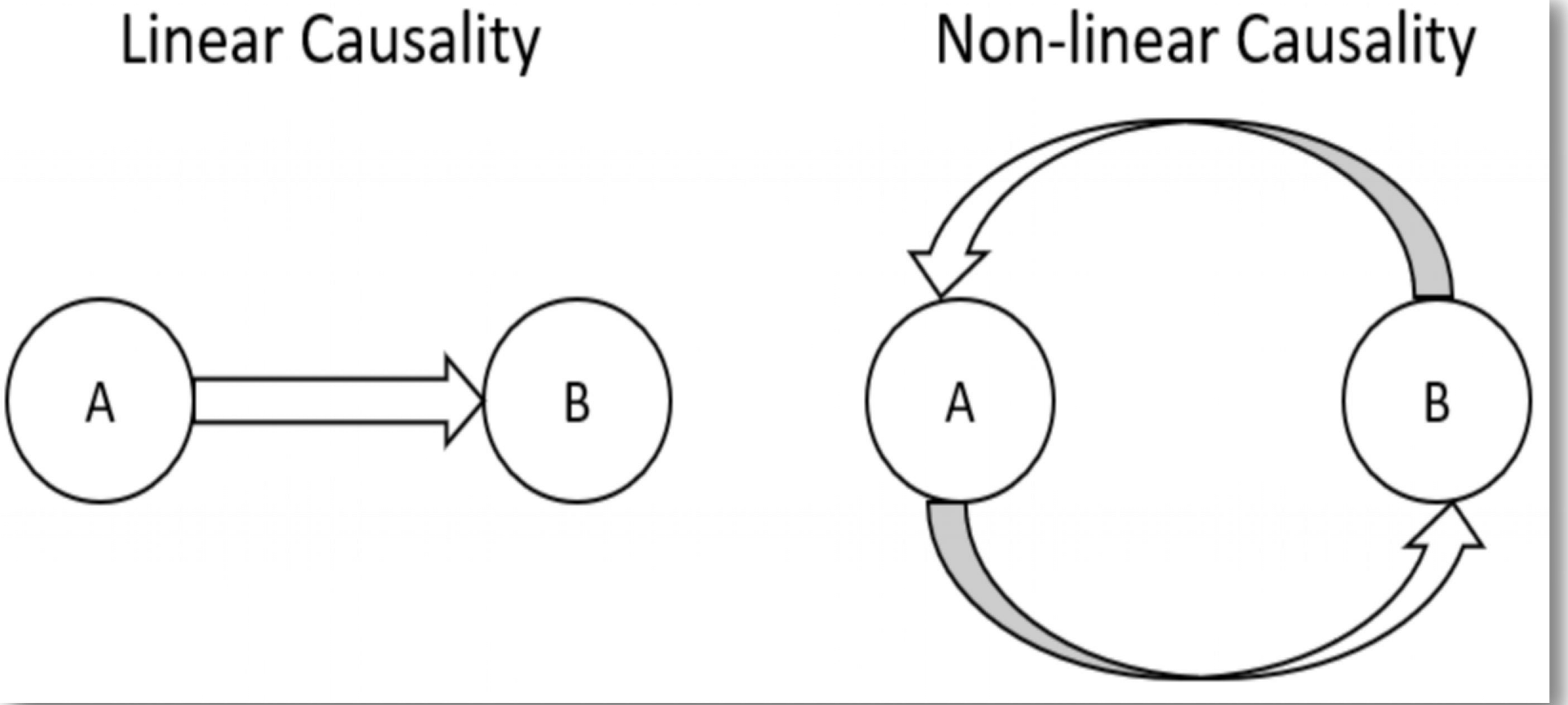


Deterministic Causality

EXAMPLE OF SUFFICIENT CAUSE

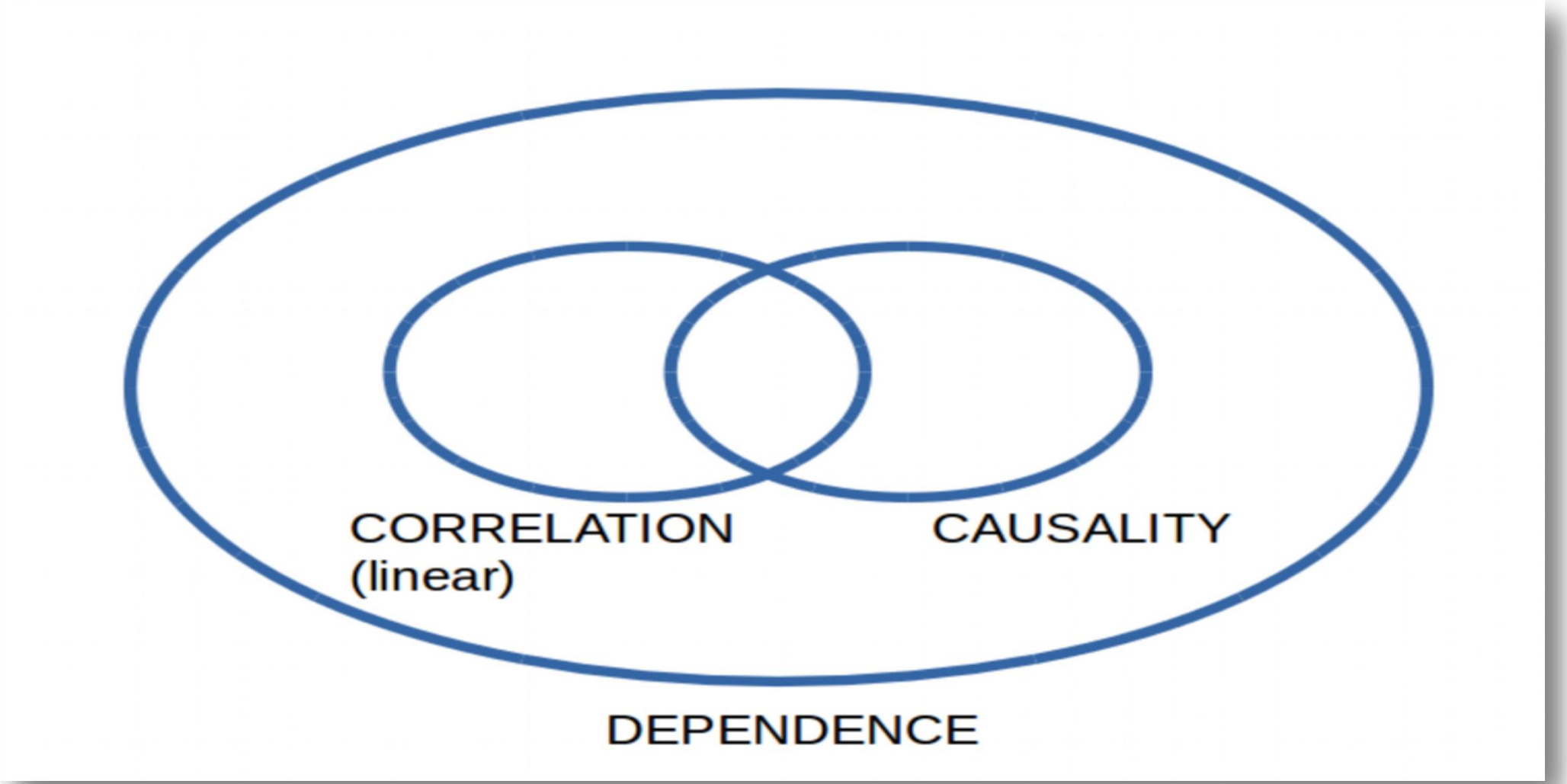
Sufficient causes are very rare in medicine, because it is exceptional that one exposure is by itself enough to cause disease. Usually exposures are much more common than the diseases they cause. Only about 5% of people who smoke get lung cancer. The measles virus virtually always causes people to get clinical measles, and rabies infection is always fatal.

Linear & Non-Linear Causality



Correlation & Causality

Correlation is defined as the statistical association between two variables.



Correlation & Causality

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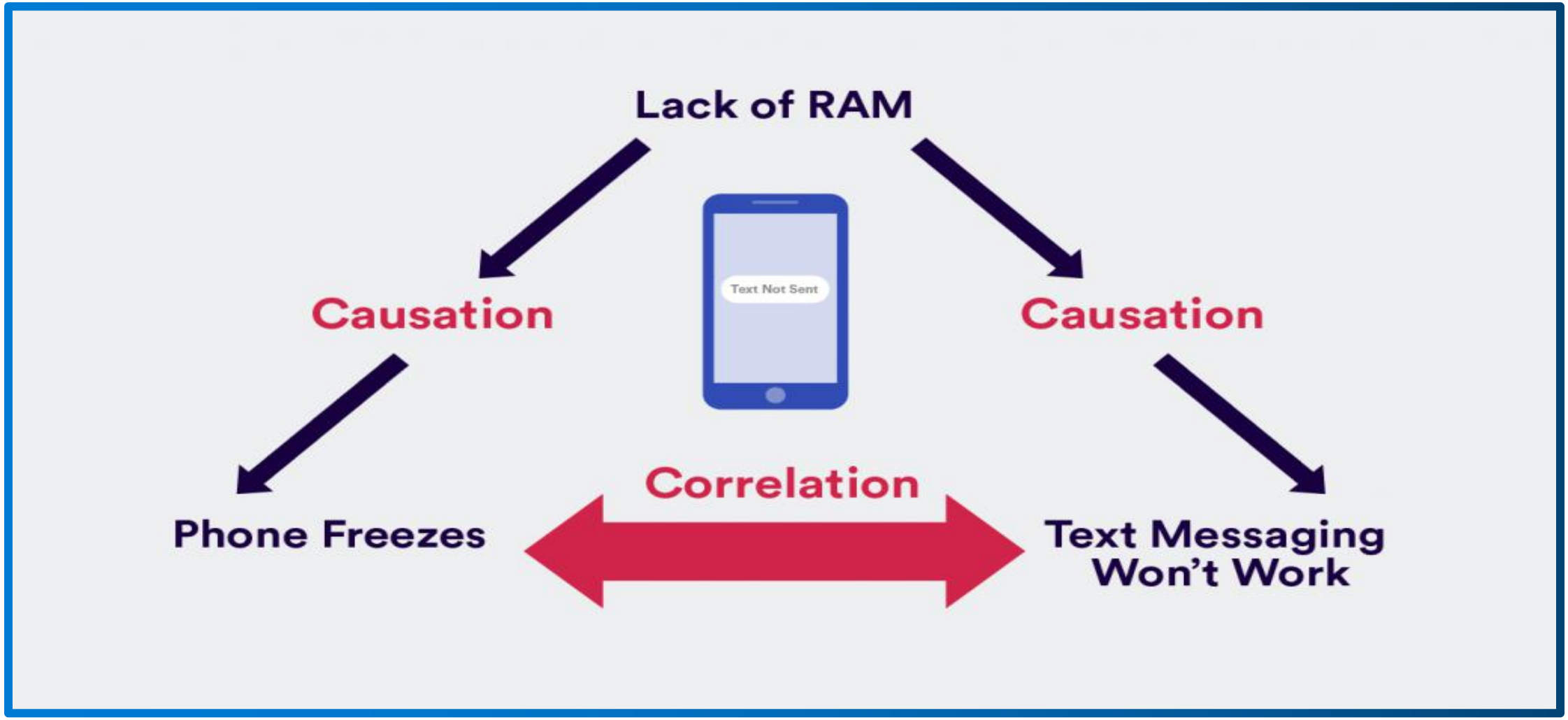


Criteria for Causal Association

Bradford Hill's criteria for making causal inferences-

1. Strength of association
2. Dose-Response relationship
3. Lack of temporal ambiguity
4. Consistency of findings
5. Biologic plausibility
6. Coherence of evidence
7. Specificity of association

Temporal Association

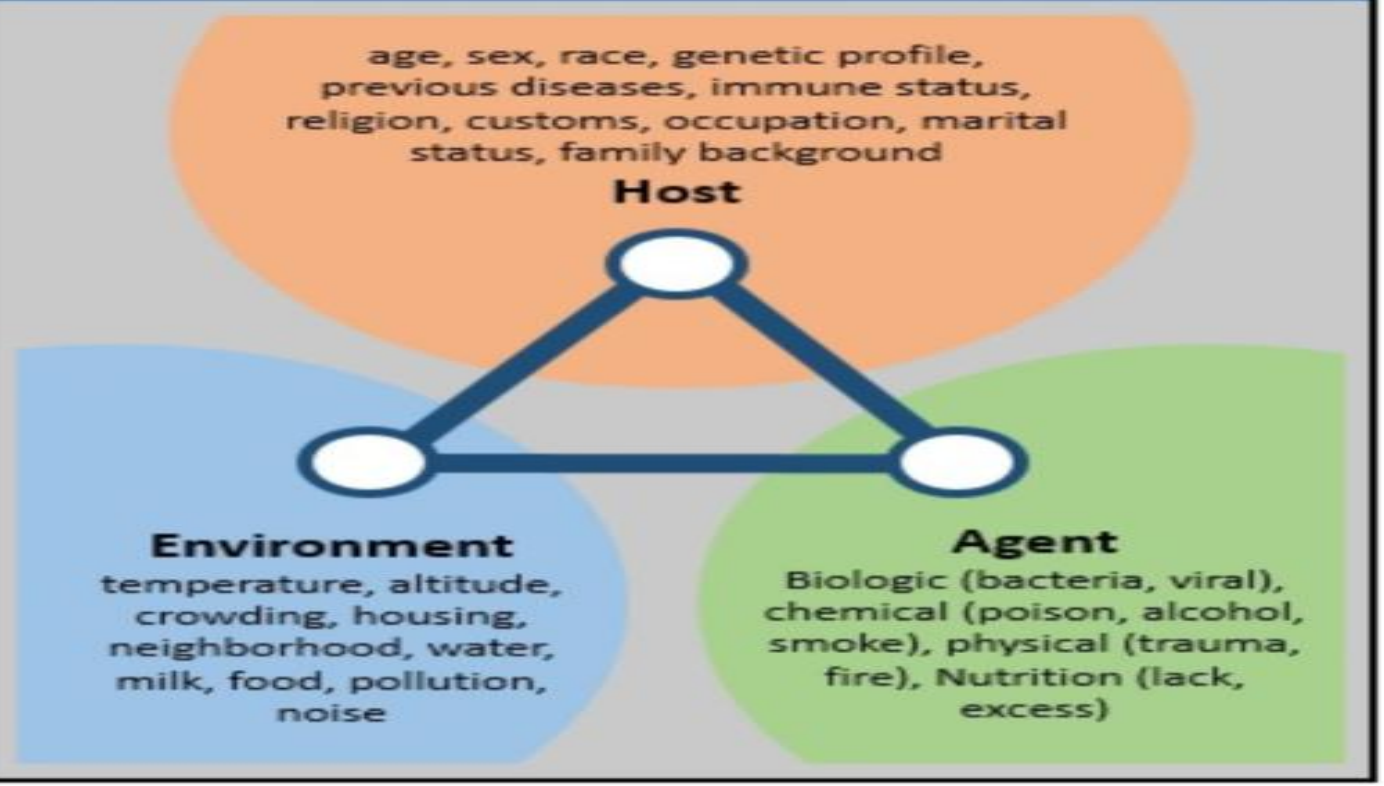
- Exposure to causative factor must occur before the onset of disease.
- This criteria is basic to the causal association.
- Establishment of temporal association is easy in acute communicable diseases
- It is difficult to establish temporal sequence in chronic insidious non communicable diseases as to which came first.
- The consumption of cigarette smoking preceded by 30 years to the increase in the death rates due to lung cancer. Theses observations are compatible with the long latent period pathogenesis of carcinogenesis .

Hill's Criteria for Causal Relation

- Strength of association
- Consistency of findings
- Specificity of association
- Temporal sequence
- Biological gradient (dose-response)
- Biological plausibility
- Coherence with established facts
- Experimental evidence

Epidemiological Triangle

- Basic model to study health problems
- 3 factors
  - Host
  - Environment
  - Agent
- Disease is produced by exposure of a susceptible host to an noxious agent in the presence of environmental factors that aid or hinder agents of disease



- Hills Criteria of Causality
- multivariate causality
- deterministic causality
- probabilistic causality

Causal Inference in Epidemiology

Bridging the gap between our ideas and our observations.

Criteria:

- Strength of association
- Consistency of findings
- Specificity of association
- Temporality (lack of ambiguity)
- Biologic gradient (dose-response effect)
- Biologic plausibility of the hypothesis
- Coherence of evidence
- Experimental evidence

Introducing DoWhy

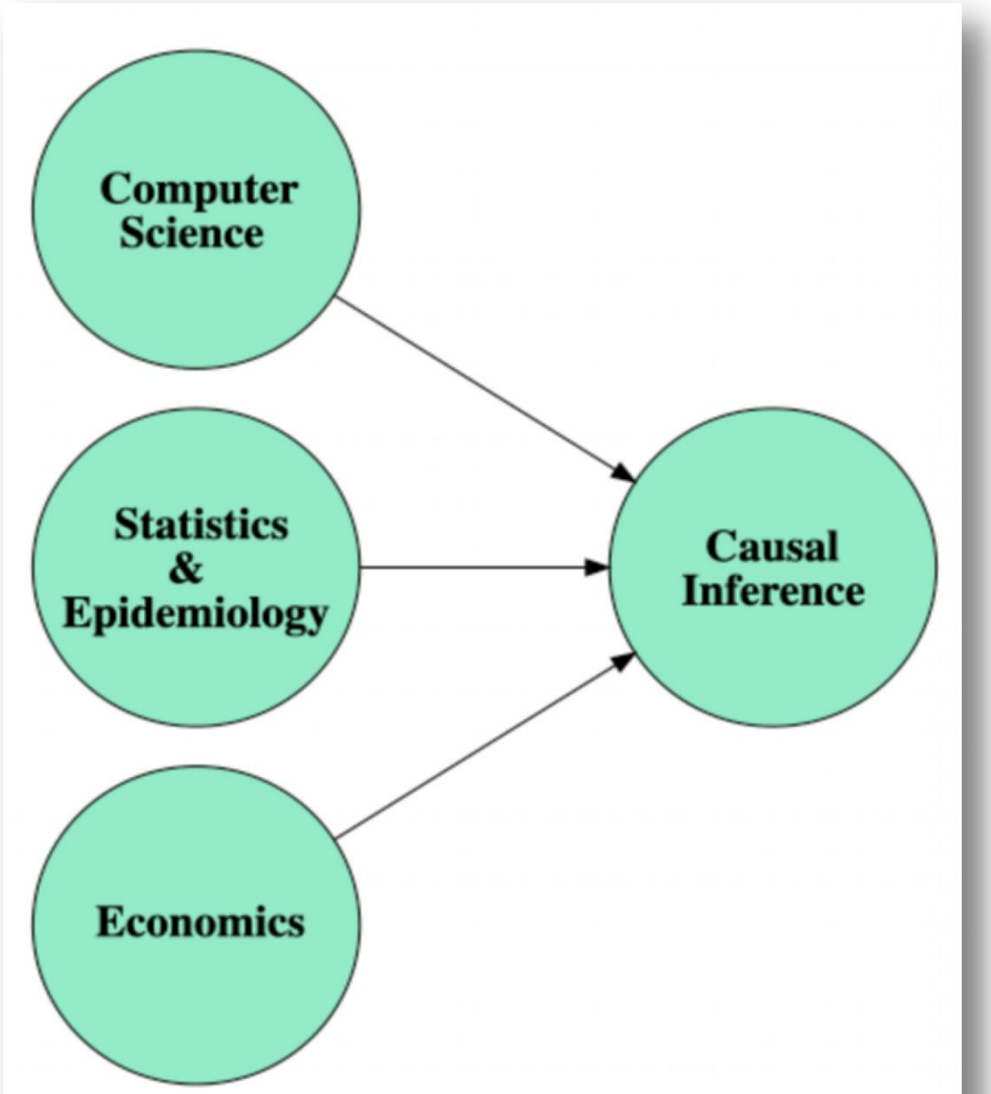
The human mind has a remarkable ability to associate causes with a specific event. *From the outcome of an election to an object dropping on the floor, we are constantly associating chains of events that cause a specific effect.* Neuropsychology refers to this cognitive ability as **causal reasoning**. *Computer science and economics study a specific form of **causal reasoning** known as **causal inference** which focuses on exploring relationships between two observed variables*. Over the years, ***machine learning*** has produced many methods for ***causal inference*** but they remain mostly difficult to use in mainstream applications. Recently, Microsoft Research open sourced DoWhy, a framework for ***causal thinking and analysis***.

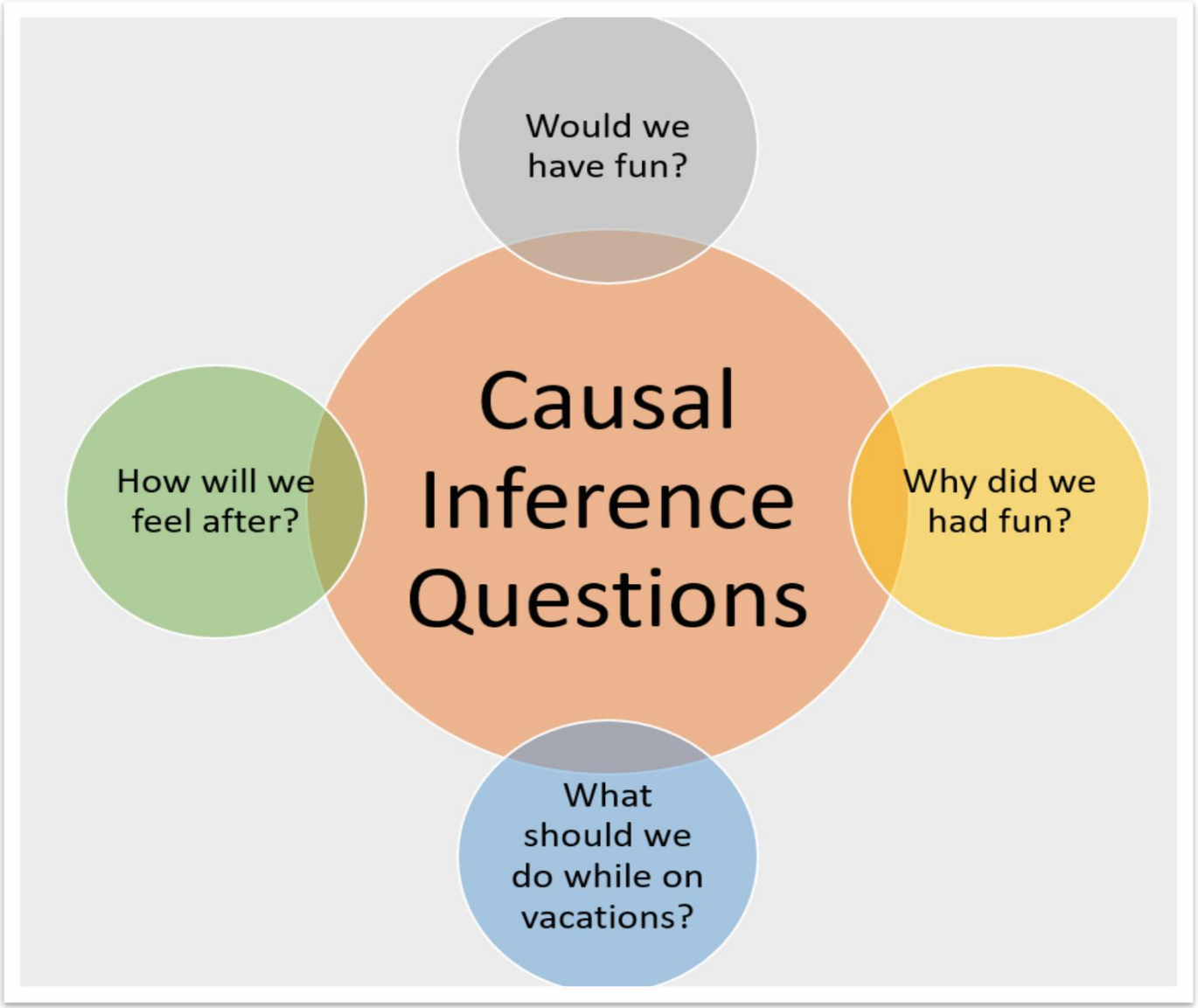
The challenge with causal inference

The challenge with ***causal inference*** is not that is a new discipline, quite the opposite, but that the current methods represent a very small and simplistic version of ***causal reasoning***. Most models that try to ***connect causes*** such as linear regression rely on empirical analysis that makes some assumption about the data. **Pure causal inference** relies on counterfactual analysis which is a closer representation to how humans make decisions. Imagine a scenario in which you are traveling with your families for vacations to an unknown destination. Before and after the vacation you are wrestling with a few counterfactual questions:

1.https://towardsdatascience.com/introducing-dowhy-cc58b75d61ac

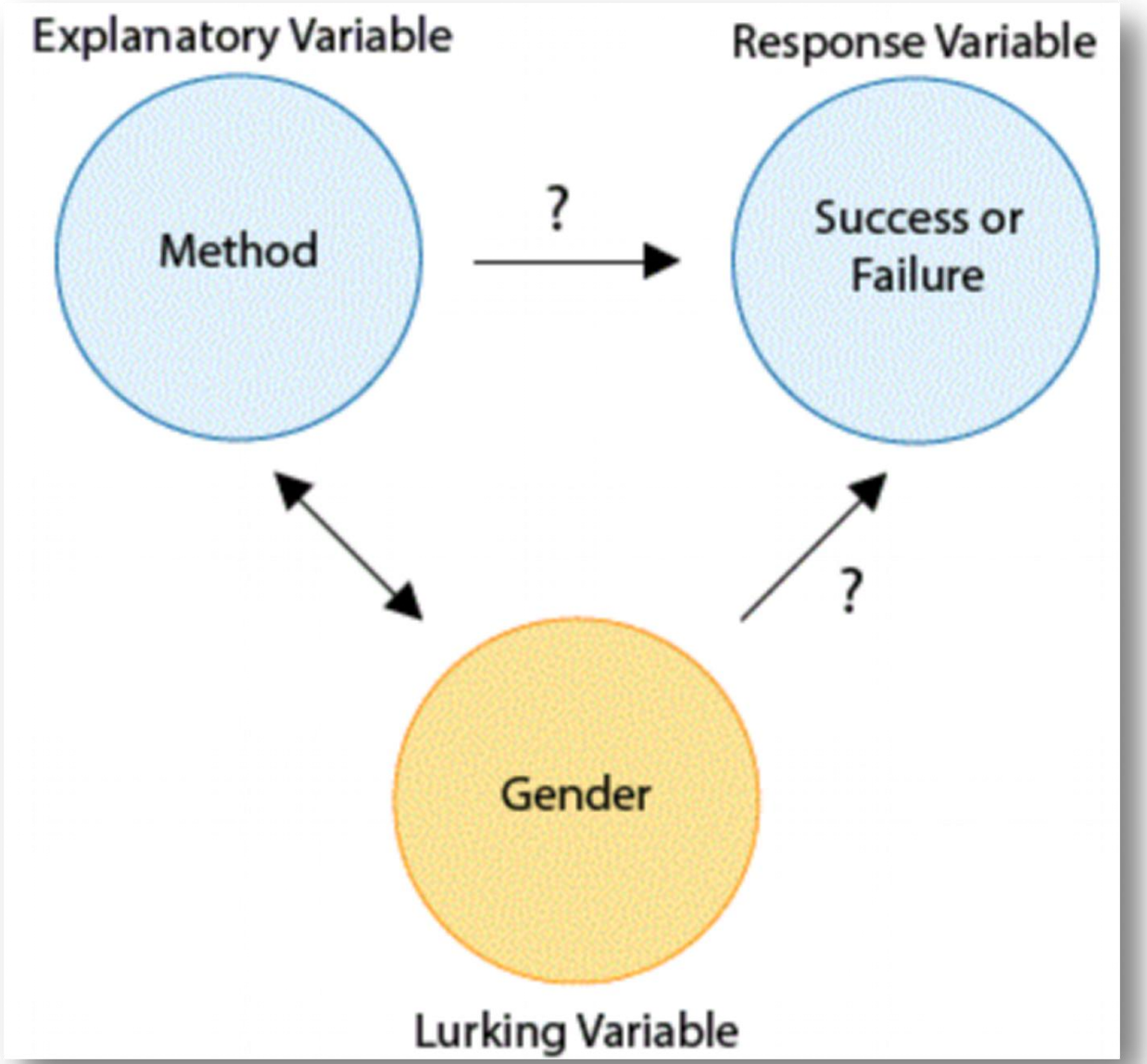
Causal Inference & Questions





https://aiws.net/practicing-principles/modern-causal-inference/augmenting/on-media-augmenting/introducing-dowhy/

Variables for causal inference



Does simple linear regression imply causation?

Correlation does not imply causation but instead the strength and direction of the relationship.

There is nothing explicit in the mathematics of **regression** that state causal relationships, and hence one need not explicitly interpret the slope *(strength and direction)* nor the **p-values** (i.e. the probability a relation as strong as or stronger would have been observed if the relationship were zero in the population) in a causal manner.

Any QUESTIONS? or COMMENTS??

f o r

Thank you for joining..

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