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Causal inference and study design

Research article

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Abstract

Background:

Causal inference based on logically consistent mathematical methods requires suitable, high-quality data and a corresponding study design. However, the question remains so far unanswered which aspects need to be considered by a design of a study in order to ensure the possibility to detect cause-effect relationships.

Methods:

In this article, we focus on the mathematical requirements of a study design of experimental or non-experimental studies whose aim is to identify causal relationship between events.

Results:

A relatively new proof of the relationship between study design and the possibility of causal inference has been provided. The possible relationship between relative risk, odds ratio and causality has been worked out.

Conclusion:

The mathematical proof described here is of use to improve the study design of experimental and non-experimental studies.

Keywords: Necessary condition; Conditio sine qua non; Cause; Effect; Causation; Study design

1. Introduction

Causation(Barukčić, 1989, 1997, 2005, 2016b, 2017a,c, 2021d, Thompson, 2006) is an essential concept in science, and more particularly in clinical medical research. In clinical medical research, many times, causality is demonstrated by an experiment or better to say by a randomized controlled trial [1] (RCT). Out of the wide variety of reasons, often, an RCT cannot be conducted. Thus far, under conditions when an experiment cannot be conducted, an observational study need to be performed.

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There are a number of different methods [2] [3] which attempt to infer causality [4] , [5] from experimental and non-experimental or observational data. However, these methods [6] , [7] , [8] differ extremely and are highly unreliable, especially in the absence of experimental data. Taken into account the planning of a study, often the difficulties to infer a causal relationship between events increase. Many times, the study design of (medical) studies is inappropriate because the prerequisites of a correct study design are not applied strictly enough or completely ignored, while the conclusion drawn by methods [9] used to demonstrate a causal relationship under these circumstances are in vain. Such circumstances might provoke some unjustified confusion about a natural concept of causation. Nonetheless, a far-reaching and much more difficult question is, what are the prerequisites of a correct study design [10] , [11] , [12] , [13] , [14] and can causality [15] be defined or demonstrated by medical studies at all, and to what extent? The methods developed here can be used to derive causal inferences from experimental or non-experimental (observational) studies.

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2. Material and methods

Scientific knowledge and objective reality are deeply interrelated. Seen by light, grey is never merely simply grey, and many paths may lead to climb up a certain mountain. In the following of this paper, we will reanalyse the relationship between oxygen and human survival in many ways and under different circumstances to reach the main goal.

2.1. Methods

Definitions should help us to provide and assure a systematic approach to a mathematical formulation of the relationship of a necessary condition. It also goes without the need of further saying that a definition must be logically consistent and correct.

2.1.1. Random variables

Let a **random variable**(Gosset, 1914) X denote something like a function defined on a probability space, which itself maps from the sample space(Neyman and Pearson, 1933) to the real numbers.

2.1.2. The Expectation of a Random Variable

Definition 2.1 (**The First Moment Expectation of a Random Variable**). *Summaries of an entire distribution of a random variable(see Kolmogorov, Andreĭ Nikolaevich, 1950, p. 22) X, such as the expected value, or average value, are useful in order to identify where X is expected to be without describing the entire distribution. For practical and other reasons, we shall limit ourselves here to discrete random variables, while the basic properties of the expectation value of a random variable X will not be investigated. Thus far, let X be a discrete random variable with the probability p(X). The first moment expectation value (see Huygens and van Schooten, 1657, Kolmogorov, Andreĭ Nikolaevich, 1950, LaPlace, 1812, Whitworth, 1901) of X, denoted by E(X), is a number defined as follows:*

$$E(X) \equiv p(X) \times X \tag{1}$$

The first moment expectation value squared of a random variable X follows as

$$\begin{aligned} E(X)^2 &\equiv p(X) \times X \times p(X) \times X \\ &\equiv p(X) \times p(X) \times X \times X \\ &\equiv (p(X) \times X)^2 \\ &\equiv E(X) \times E(X) \end{aligned} \tag{2}$$

Definition 2.2 (**The Second Moment Expectation of a Random Variable**). *The second(see Kolmogorov, Andreĭ Nikolaevich, 1950, p. 42) moment expectation value (or more or less arithmetic mean) of a (large) number of independent realizations of a random variable X follows as:*

$$\begin{aligned} E\left(X^2\right) &\equiv p\left(X\right) \times X^2 \\ &\equiv \left(p\left(X\right) \times X\right) \times X \\ &\equiv E\left(X\right) \times X \\ &\equiv X \times E\left(X\right) \end{aligned} \tag{3}$$

Definition 2.3 (**The n-th Moment Expectation of a Random Variable**). *The n-th(see Barukčić, 2020a, 2021d) moment expectation value of a (large) number of independent realizations of a random variable X follows as:*

$$\begin{aligned} E\left(X^n\right) &\equiv p\left(X\right) \times X^n \\ &\equiv \left(p\left(X\right) \times X\right) \times X^{n\text{-}1} \\ &\equiv E\left(X\right) \times X^{n\text{-}1} \end{aligned} \tag{4}$$

2.1.3. Probability of a Random Variable

The probability p(X) of a random variable X follows as (see equation 1)

$$\begin{aligned} p\left(X\right) &\equiv \frac{X \times p\left(X\right)}{X} \equiv \frac{E\left(X\right)}{X} \\ &\equiv \frac{X \times X \times p\left(X\right)}{X \times X} \equiv \frac{E\left(X^2\right)}{X^2} \\ &\equiv \frac{E\left(X\right) \times E\left(X\right)}{E\left(X\right) \times X} \equiv \frac{E\left(X\right)^2}{E\left(X^2\right)} \\ &\equiv \Psi\left(X\right) \times \Psi^*\left(X\right) \end{aligned} \tag{5}$$

where $\Psi\left(X\right)$ is the wave-function of X, $\Psi^*\left(X\right)$ is the complex conjugate wave-function of X.

2.1.4. Variance of a Random Variable

Definition 2.4 (**The Variance of a Random Variable**). *Johann Carl Friedrich Gauß (1777-1855) introduced the normal distribution and the error of mean squared in his 1809 monograph(see Gauß, Carl Friedrich, 1809). In the following, Karl Pearson (1857-1936) coined the term "standard deviation"in 1893. Pearson is writing: "Then σ will be termed its standard-deviation (error of mean square)."(see Pearson, 1894, p. 80). Finally, the term variance was introduced by Sir Ronald Aylmer Fisher (1890-1962) in the year 1918.*

> *"The ... deviations of a ... measurement from its mean ... may be ... measured by the standard deviation corresponding to the square root of the mean square error ... It is ... desirable* ***in analysing the causes*** *... to deal with the square of the standard deviation as the measure of variability. We shall term this quantity the Variance... "*
>
> *(see Fisher, Ronald Aylmer, 1919, p. 399)*

The deviation of a random variable X from its population mean or sample mean E(X) has a central role in statistics and is one important measure of dispersion. The variance $\sigma(X)^2$ *(see Kolmogorov, Andreť Nikolaevich, 1950, p. 42), the second central moment of a distribution, is the expectation value of the squared deviation of a random variable X from its own expectation value E(X) and is determined in general as (see equation 3):*

$$\begin{aligned} \sigma(X)^2 &\equiv E\left(X^2\right) - E(X)^2 \\ &\equiv (X \times E(X)) - E(X)^2 \\ &\equiv E(X) \times (X - E(X)) \\ &\equiv E(X) \times E(\underline{X}) \end{aligned} \tag{6}$$

while $E(\underline{X}) \equiv X - E(X)$. In particular, variance is a specific statistical method which is of help to evaluate hypotheses in the light of empirical facts. But as a mathematical tool or method, variance is also a science specific description of a certain part of objective reality. In this context, as a general mathematical principle, one fundamental meaning of variance is to provide a link between something and its own other.

> "The variance in this sense is a measure of the inner contradictions of a random variable, of changes, of struggle within this random variable itself, or the greater $\sigma(X)^2$ of a random variable, the greater the inner contradictions of this random variable. "
>
> (see Barukčić, 2006a, p. 57)

All things considered, we can safely say that, on the whole, **the variance is a mathematical description of the philosophical notion of the inner contradiction of a random variable X** (see Hegel, Georg Wilhelm Friedrich, 1812, 1813, 1816) . Based on equation 6, it is

$$E\left(X^2\right) \equiv E\left(X\right)^2 + \sigma\left(X\right)^2 \tag{7}$$

or

$$\frac{E\left(X\right)^2}{E\left(X^2\right)} + \frac{\sigma\left(X\right)^2}{E\left(X^2\right)} \equiv p\left(X\right) + \frac{\sigma\left(X\right)^2}{E\left(X^2\right)} \equiv +1 \tag{8}$$

In other words, the variance (see Barukčić, 2006b) of a random variable is a determining part of the probability of a random variable. The wave function Ψ follows in general, as

$$\begin{aligned}
\Psi\left(X\right) &\equiv \frac{1}{\Psi^*\left(X\right)} - \frac{\sigma\left(X\right)^2}{\left(\Psi^*\left(X\right) \times E\left(X^2\right)\right)} \\
&\equiv \frac{\left(E\left(X^2\right) - \sigma\left(X\right)^2\right)}{\left(\Psi^*\left(X\right) \times E\left(X^2\right)\right)} \\
&\equiv \frac{1}{\left(\Psi^*\left(X\right) \times E\left(X^2\right)\right)} \times \left(E\left(X^2\right) - \sigma\left(X\right)^2\right) \\
&\equiv \frac{1}{\left(\Psi^*\left(X\right) \times E\left(X^2\right)\right)} \times E\left(X\right)^2 \\
&\equiv \frac{1}{\Psi^*\left(X\right)} \times \frac{E\left(X\right)^2}{E\left(X^2\right)} \\
&\equiv \frac{1}{\Psi^*\left(X\right) \times X} \times E\left(X\right)
\end{aligned} \tag{9}$$

The wave function (see Born, 1926) of a quantum-mechanical system is a central determining part of the Schrödinger wave equation (see Schrödinger, Erwin Rudolf Josef Alexander, 1926, 1929, 1952).

Definition 2.5 (**The First Moment Expectation of a Random Variable of $\underline{X}$ (anti X)**). *In general, let $E\left(\underline{X}\right)$ be defined as*

$$E\left(\underline{X}\right) \equiv X - E\left(X\right) \equiv X - \left(X \times p\left(X\right)\right) \tag{10}$$

and denote an expectation value of a (discrete) random variable anti X with the probability

$$p(\underline{X}) \equiv 1 - p\left(X\right) \tag{11}$$

The first moment expectation value (see Huygens and van Schooten, 1657, Kolmogorov, Andreĭ Nikolaevich, 1950, LaPlace, 1812, Whitworth, 1901) of anti X, denoted as $E(\underline{X})$, is a number defined as follows:

$$E\left(\underline{X}\right) \equiv X - \left(X \times p\left(X\right)\right) \equiv X \times \left(1 - p\left(X\right)\right) \equiv X \times p\left(\underline{X}\right) \tag{12}$$

The first moment expectation value squared of a random variable anti X follows as

$$\begin{aligned} E\left(\underline{X}\right)^2 &\equiv p\left(\underline{X}\right) \times X \times p\left(\underline{X}\right) \times X \\ &\equiv p\left(\underline{X}\right) \times p\left(\underline{X}\right) \times X \times X \\ &\equiv \left(p\left(\underline{X}\right) \times X\right)^2 \\ &\equiv E\left(\underline{X}\right) \times E\left(\underline{X}\right) \end{aligned} \tag{13}$$

Definition 2.6 (**The Second Moment Expectation of a Random Variable of $\underline{\mathbf{X}}$ (anti X)**). *The second(see Kolmogorov, Andreĭ Nikolaevich, 1950, p. 42) moment expectation value (or more or less arithmetic mean) of a (large) number of independent realizations of a random variable anti X follows as:*

$$\begin{aligned} E\left(\underline{X}^2\right) &\equiv p\left(\underline{X}\right) \times X^2 \\ &\equiv \left(p\left(\underline{X}\right) \times X\right) \times X \\ &\equiv E\left(\underline{X}\right) \times X \\ &\equiv X \times E\left(\underline{X}\right) \end{aligned} \tag{14}$$

Definition 2.7 (**The n-th Moment Expectation of a Random Variable of $\underline{\mathbf{X}}$ (anti X)**). *The n-th(see Barukčić, 2020a, 2021d) moment expectation value of a (large) number of independent realizations of a random variable anti X follows as:*

$$\begin{aligned} E\left(\underline{X}^n\right) &\equiv p\left(\underline{X}\right) \times X^n \\ &\equiv \left(p\left(\underline{X}\right) \times X\right) \times X^{n\text{-}1} \\ &\equiv E\left(\underline{X}\right) \times X^{n\text{-}1} \end{aligned} \tag{15}$$

2.1.5. Bernoulli distribution

A single event distribution is more or less a discrete probability distribution of any random variable X which takes a certain (observer independent) single value X_t at a **Bernoulli trial** (Uspensky, 1937, p. 45) (period of time) t with the probability $p(X_t)$. The same random variable X takes a certain single anti value $\underline{X}_t$ at a Bernoulli trial (period of time) t with the probability 1-$p(X_t)$. There are conditions in nature where a random variable X can take only the values either +0 or +1 (see Birnbaum, 1961). Under these conditions, the random variable X takes the value 1 with probability $p(X_t = +1)$ and the value 0 with probability $q(X_t = +0) = 1 - p(X_t = +1)$ while the single event distribution passes over into the **Bernoulli distribution**, named after Swiss mathematician Jacob Bernoulli (Bernoulli, 1713). Less formally, many times, the Bernoulli distribution is represented by a (possibly not biased) coin toss where 1 and 0 would represent 'heads'and 'tails'(or vice versa), respectively. However, the relationship between random variables (Gosset, 1914) can be investigated by many (Gosset, 1908) methods, including the tools of probability theory, too.

Definition 2.8 (Two by two table of single event random variables).

The two by two or contingency table which has been introduced by Karl Pearson (Pearson, 1904b) in 1904 harbours still a large variety of topics and debates. Central to this is the problem to apply the laws of classical logic on data sets, which concerns the justification of inferences which extrapolate from sample data to general facts. Nevertheless, a contingency table is still an appropriate theoretical model too for studying the relationships between random variables, including *Bernoulli (Bernoulli, 1713) (i.e. +0/+1) distributed random variables* existing or occurring at the same *Bernoulli trial* (Uspensky, 1937) (period of time) t.

In this context, let a random variable A at the *Bernoulli trial* (Uspensky, 1937) (period of time) t, denoted by A_t, indicate a risk factor, a condition, a cause et cetera and occur or exist with the probability $p(A_t)$ at the *Bernoulli trial* (Uspensky, 1937) (period of time) t. Let $E(A_t)$ denote the expectation value of A_t. In general it is

$$p(A_t) \equiv p(a_t) + p(b_t) \tag{16}$$

The expectation value $E(A_t)$ follows as

$$\begin{aligned} E(A_t) &\equiv A_t \times p(A_t) \\ &\equiv A_t \times (p(a_t) + p(b_t)) \\ &\equiv (A_t \times p(a_t)) + (A_t \times p(b_t)) \\ &\equiv E(a_t) + E(b_t) \end{aligned} \tag{17}$$

Under conditions of +0/+1 distributed Bernoulli random variables it is

$$\begin{aligned} E(A_t) &\equiv A_t \times p(A_t) \\ &\equiv (+0+1) \times p(A_t) \\ &\equiv p(A_t) \\ &\equiv p(a_t) + p(b_t) \end{aligned} \tag{18}$$

Furthermore, it is

$$p\left(\underline{A}_t\right) \equiv p\left(c_t\right) + p\left(d_t\right) \equiv \left(1 - p\left(A_t\right)\right) \tag{19}$$

The expectation value E($\underline{A}_t$) is given as

$$\begin{aligned} E\left(\underline{A}_t\right) &\equiv A_t \times \left(1 - p\left(A_t\right)\right) \\ &\equiv A_t \times \left(p\left(c_t\right) + p\left(d_t\right)\right) \\ &\equiv \left(A_t \times p\left(c_t\right)\right) + \left(A_t \times p\left(d_t\right)\right) \\ &\equiv E\left(c_t\right) + E\left(d_t\right) \end{aligned} \tag{20}$$

Under conditions of +0/+1 distributed Bernoulli random variables we obtain

$$\begin{aligned} E\left(\underline{A}_t\right) &\equiv A_t \times \left(1 - p\left(A_t\right)\right) \\ &\equiv \left(+0 + 1\right) \times \left(1 - p\left(A_t\right)\right) \\ &\equiv \left(1 - p\left(A_t\right)\right) \\ &\equiv p\left(c_t\right) + p\left(d_t\right) \end{aligned} \tag{21}$$

Let a random variable B at the *Bernoulli trial* (Uspensky, 1937) (period of time) t, denoted by B_t, indicate an outcome, a conditioned, an effect et cetera and occur or exist with the probability $p(B_t)$ at the *Bernoulli trial* (Uspensky, 1937) (period of time) t. Let $E(B_t)$ denote the expectation value of B_t. In general it is

$$p\left(B_t\right) \equiv p\left(a_t\right) + p\left(c_t\right) \tag{22}$$

The expectation value $E(B_t)$ is given by the equation

$$\begin{aligned} E\left(B_t\right) &\equiv B_t \times p\left(B_t\right) \\ &\equiv B_t \times \left(p\left(a_t\right) + p\left(c_t\right)\right) \\ &\equiv \left(B_t \times p\left(a_t\right)\right) + \left(B_t \times p\left(c_t\right)\right) \\ &\equiv E\left(a_t\right) + E\left(c_t\right) \end{aligned} \tag{23}$$

Under conditions of +0/+1 distributed Bernoulli random variables it is

$$\begin{aligned} E\left(B_t\right) &\equiv B_t \times p\left(B_t\right) \\ &\equiv \left(+0 + 1\right) \times p\left(B_t\right) \\ &\equiv p\left(B_t\right) \\ &\equiv p\left(a_t\right) + p\left(c_t\right) \end{aligned} \tag{24}$$

Furthermore, it is

$$p\left(\underline{B}_t\right) \equiv p\left(b_t\right) + p\left(d_t\right) \equiv \left(1 - p\left(B_t\right)\right) \tag{25}$$

The expectation value E($\underline{B}_t$) is given by the equation

$$\begin{aligned} E\left(\underline{B}_t\right) &\equiv B_t \times \left(1 - p\left(B_t\right)\right) \\ &\equiv B_t \times \left(p\left(b_t\right) + p\left(d_t\right)\right) \\ &\equiv \left(B_t \times p\left(b_t\right)\right) + \left(B_t \times p\left(d_t\right)\right) \\ &\equiv E\left(b_t\right) + E\left(d_t\right) \end{aligned} \tag{26}$$

Under conditions of +0/+1 distributed Bernoulli random variables it is

$$\begin{aligned} E\left(\underline{B}_t\right) &\equiv B_t \times \left(1 - p\left(B_t\right)\right) \\ &\equiv (+0+1) \times \left(1 - p\left(B_t\right)\right) \\ &\equiv \left(1 - p\left(B_t\right)\right) \\ &\equiv p\left(b_t\right) + p\left(d_t\right) \end{aligned} \tag{27}$$

Let $p(a_t)= p(A_t \wedge B_t)$ denote the joint probability distribution of A_t and B_t at the same Bernoulli trial (period of time) t. In general, it is

$$\begin{aligned} E\left(a_t\right) &\equiv E\left(A_t \wedge B_t\right) \\ &\equiv \left(A_t \times B_t\right) \times p(A_t \wedge B_t) \\ &\equiv \left(A_t \times B_t\right) \times p(a_t) \end{aligned} \tag{28}$$

Under conditions of +0/+1 distributed Bernoulli random variables, it is

$$\begin{aligned} E\left(a_t\right) &\equiv E\left(A_t \wedge B_t\right) \\ &\equiv \left(A_t \times B_t\right) \times p(A_t \wedge B_t) \\ &\equiv ((+0+1) \times (+0+1)) \times p(A_t \wedge B_t) \\ &\equiv p(A_t \wedge B_t) \\ &\equiv p\left(a_t\right) \end{aligned} \tag{29}$$

Let $p(b_t)= p(A_t \wedge \neg B_t)$ denote the joint probability distribution of A_t and not B_t at the same Bernoulli trial (period of time) t. In general, it is

$$\begin{aligned} E\left(b_t\right) &\equiv E\left(A_t \wedge \neg B_t\right) \\ &\equiv \left(A_t \times \neg B_t\right) \times p(A_t \wedge \neg B_t) \\ &\equiv \left(A_t \times \neg B_t\right) \times p(b_t) \end{aligned} \tag{30}$$

Under conditions of +0/+1 distributed Bernoulli random variables, it is

$$\begin{aligned} E\left(b_t\right) &\equiv E\left(A_t \wedge \neg B_t\right) \\ &\equiv \left(A_t \times \neg B_t\right) \times p(A_t \wedge \neg B_t) \\ &\equiv ((+0+1) \times (+0+1)) \times p(A_t \wedge \neg B_t) \\ &\equiv p(A_t \wedge \neg B_t) \\ &\equiv p\left(b_t\right) \end{aligned} \tag{31}$$

Let $p(c_t)= p(\neg A_t \wedge B_t)$ denote the joint probability distribution of not A_t and B_t at the same Bernoulli trial (period of time) t. In general, it is

$$\begin{aligned} E\left(c_t\right) &\equiv E\left(\neg A_t \wedge B_t\right) \\ &\equiv \left(\neg A_t \wedge B_t\right) \times p\left(\neg A_t \wedge B_t\right) \\ &\equiv \left(\neg A_t \wedge B_t\right) \times p(c_t) \end{aligned} \tag{32}$$

Under conditions of +0/+1 distributed Bernoulli random variables, it is

$$\begin{aligned} E(c_t) &\equiv E(\neg A_t \wedge B_t) \\ &\equiv (\neg A_t \times B_t) \times p(\neg A_t \wedge B_t) \\ &\equiv ((+0+1) \times (+0+1)) \times p(\neg A_t \wedge B_t) \\ &\equiv p(\neg A_t \wedge B_t) \\ &\equiv p(c_t) \end{aligned} \tag{33}$$

Let $p(d_t) = p(\neg A_t \wedge \neg B_t)$ denote the joint probability distribution of not A_t and not B_t at the same Bernoulli trial (period of time) t. In general, it is

$$\begin{aligned} E(d_t) &\equiv E(\neg A_t \times \neg B_t) \\ &\equiv (\neg A_t \times \neg B_t) \times p(\neg A_t \wedge \neg B_t) \\ &\equiv (\neg A_t \times \neg B_t) \times p(d_t) \end{aligned} \tag{34}$$

Under conditions of +0/+1 distributed Bernoulli random variables, it is

$$\begin{aligned} E(d_t) &\equiv E(\neg A_t \wedge \neg B_t) \\ &\equiv (\neg A_t \times \neg B_t) \times p(\neg A_t \wedge \neg B_t) \\ &\equiv ((+0+1) \times (+0+1)) \times p(\neg A_t \wedge \neg B_t) \\ &\equiv p(\neg A_t \wedge \neg B_t) \\ &\equiv p(d_t) \end{aligned} \tag{35}$$

In general, it is

$$p(a_t) + p(b_t) + p(c_t) + p(d_t) \equiv +1 \tag{36}$$

Table 1 provide us with an overview of the definitions above.

Table 1. The two by two table of Bernoulli random variables

		Conditioned B_t		
		TRUE	FALSE	
Condition A_t	TRUE	$p(a_t)$	$p(b_t)$	$p(A_t)$
	FALSE	$p(c_t)$	$p(d_t)$	$p(\underline{A}_t)$
		$p(B_t)$	$p(\underline{B}_t)$	+1

2.1.6. Binomial random variables

The binomial distribution (see Cramér, 1937) with parameters n and p has been developed by the Swiss mathematician Jakob Bernoulli (1655-1705) in a proof published in his 1713 book Ars Conjectandi (see Bernoulli, 1713) Part 1. In probability theory and statistics, the probability of getting exactly k successes in n independent Bernoulli trials is given by the probability mass function as

$$p\left(X_{\mathrm{t}}=k\right) \equiv \binom{n}{k} \cdot p^{k} \cdot q^{n-k} \tag{37}$$

is $\binom{n}{k}=\frac{n!}{k!(n-k)!}$ the binomial coefficient while the cumulative distribution function is given as

$$p\left(X_{\mathrm{t}} \leq k\right) \equiv 1-p\left(X_{\mathrm{t}}>k\right) \equiv \sum_{t=0}^{k} \binom{n}{t} \cdot p^{t} \cdot q^{n-t} \tag{38}$$

or as

$$p\left(X_{\mathrm{t}}>k\right) \equiv 1-p\left(X_{\mathrm{t}} \leq k\right) \equiv 1-\sum_{t=0}^{k} \binom{n}{t} \cdot p^{t} \cdot q^{n-t} \tag{39}$$

Furthermore, it is

$$p\left(X_{\mathrm{t}}<k\right) \equiv 1-p\left(X_{\mathrm{t}} \geq k\right) \equiv \sum_{t=0}^{k-1} \binom{n}{t} \cdot p^{t} \cdot q^{n-t} \tag{40}$$

or

$$p\left(X_{\mathrm{t}} \geq k\right) \equiv 1-p\left(X_{\mathrm{t}}<k\right) \equiv 1-\sum_{t=0}^{k-1} \binom{n}{t} \cdot p^{t} \cdot q^{n-t} \tag{41}$$

The binomial distribution is the mathematical foundation of a binomial test. The random variable X_t is counting for different things. The discrete geometric (see Feller, 1950, p. 61) distribution describes under certain circumstances the number of Bernoulli trials needed to get one success. The probability that the first occurrence of success requires k independent trials, each with success probability p, is given by the equation

$$p\left(X_{\mathrm{t}}=k\right) \equiv p \cdot q^{k-1} \tag{42}$$

The negative (see Fisher, 1941, Haldane, 1941) binomial probability is a discrete probability distribution which defines the number of successes (k) in a sequence of independent and identically distributed Bernoulli trials (n) before a specified (non-random) number of failures (denoted r) occurs. The probability mass function of the negative binomial distribution is

$$p\left(X_{\mathrm{t}}=r\right) \equiv \binom{k+r-1}{k-1} p^{k} \cdot q^{r} \tag{43}$$

where k is the number of successes, r is the number of failures, and p is the probability of success.

Definition 2.9 (Expectation value and variance of a binomial random variable).

The variance(see Pearson, 1904a, p. 66) of the binomial distribution with parameters n, the number of independent experiments each asking a yes–no question and p, the probability of a single event, is defined in contrast to Pearson (see Barukčić, Ilija, 2022) as

$$\sigma\left(X_{\mathrm{t}}\right)^{2} \equiv N \times N \times p\left(X_{\mathrm{t}}\right) \times \left(1 - p\left(X_{\mathrm{t}}\right)\right) \tag{44}$$

Definition 2.10 (Two by two table of Binomial random variables).

Let a, b, c, d, A, $\underline{\mathrm{A}}$, B, and $\underline{\mathrm{B}}$ denote expectation values. Under conditions where *the probability of an event, an outcome, a success et cetera is* ***constant*** *from Bernoulli trial to Bernoulli trial t*, it is

$$\begin{aligned} A &= N \times E\left(A_{\mathrm{t}}\right) \\ &\equiv N \times \left(A_{\mathrm{t}} \times p\left(A_{\mathrm{t}}\right)\right) \\ &\equiv N \times \left(p\left(A_{\mathrm{t}}\right) + p\left(B_{\mathrm{t}}\right)\right) \\ &\equiv N \times p\left(A_{\mathrm{t}}\right) \end{aligned} \tag{45}$$

and

$$\begin{aligned} B &= N \times E\left(B_{\mathrm{t}}\right) \\ &\equiv N \times \left(B_{\mathrm{t}} \times p\left(B_{\mathrm{t}}\right)\right) \\ &\equiv N \times \left(p\left(A_{\mathrm{t}}\right) + p\left(c_{\mathrm{t}}\right)\right) \\ &\equiv N \times p\left(B_{\mathrm{t}}\right) \end{aligned} \tag{46}$$

where N might denote the population or even the sample size. Furthermore, it is

$$a \equiv N \times \left(E\left(A_{\mathrm{t}}\right)\right) \equiv N \times \left(p\left(A_{\mathrm{t}}\right)\right) \tag{47}$$

and

$$b \equiv N \times \left(E\left(B_{\mathrm{t}}\right)\right) \equiv N \times \left(p\left(B_{\mathrm{t}}\right)\right) \tag{48}$$

and

$$c \equiv N \times \left(E\left(c_{\mathrm{t}}\right)\right) \equiv N \times \left(p\left(c_{\mathrm{t}}\right)\right) \tag{49}$$

and

$$d \equiv N \times \left(E\left(d_{\mathrm{t}}\right)\right) \equiv N \times \left(p\left(d_{\mathrm{t}}\right)\right) \tag{50}$$

and

$$a + b + c + d \equiv A + \underline{A} \equiv B + \underline{B} \equiv N \tag{51}$$

Table 2 provide us again an overview of a two by two table of Binomial random variables.

Table 2. The two by two table of Binomial random variables

		Conditioned B_t		
		TRUE	FALSE	
Condition	TRUE	a	b	A
A_t	FALSE	c	d	$\underline{A}$
		B	$\underline{B}$	N

2.1.7. Independence

Definition 2.11 (Independence).

The philosophical, mathematical(Kolmogoroff, Andreĭ Nikolaevich, 1933) and physical(Einstein, 1948) concept of independence is of fundamental(Kolmogoroff, Andreĭ Nikolaevich, 1933) importance in (natural) sciences as such. In fact, it is insightful to recall again before the mind's eye Einstein's theoretical approach to the concept of independence. "*Ohne die Annahme einer ... Unabhängigkeit der ... Dinge voneinander ... wäre physikalisches Denken ... nicht möglich.*"(Einstein, 1948). In a narrower sense, the conditio sine qua non relationship concerns itself at the end only with the case whether the presence of an event A_t (condition) enables or guarantees the presence of another event B_t (conditioned). As a result of these thoughts, another question worth asking concerns the relationship between the independence of an event A_t (a condition) and another event B_t (conditioned) and the necessary condition relationship. To be confronted with the danger of bias and equally with the burden of inappropriate conclusions drawn, another fundamental question at this stage is whether is it possible that an event A_t (a condition) is a necessary condition of event B_t (conditioned) even under circumstances where the event A_t (a condition) (a necessary condition) is independent of an event B_t (conditioned)? This question is already answered more or less to the negative (Barukčić, 2018b). An event A_t which is a necessary condition of another event B_t is equally an event without which another event (B_t) could not be, could not occur, and implies as such already a kind of dependence. However, it is not mandatory that such a kind of dependence is a causal one. Thus far, **data which provide evidence of a significant conditio sine qua non relationship between two events like A_t and B_t and equally support the hypothesis that A_t and B_t are independent of each other are more or less self-contradictory and of very restricted or of none value for further analysis**. In fact, if the opposite view would be taken as plausible, contradictions are more or less inescapable. In general, an event A_t at the Bernoulli trial t need not but can be independent of the existence or of the occurrence of another event B_t *at the same* Bernoulli trial t. Mathematically(Moivre, 1718), independence (Kolmogoroff, Andreĭ Nikolaevich, 1933) in terms of probability theory is defined at the same (period of) time (i.e. Bernoulli trial) t as

$$\begin{aligned} p\left(A_t \wedge B_t\right) &\equiv p\left(A_t\right) \times p\left(B_t\right) \equiv p\left(a_t\right) \\ &\equiv \frac{\sum_{t=1}^{N} \left(A_t \wedge B_t\right)}{N} \equiv \frac{N \times \left(p\left(a_t\right)\right)}{N} \equiv 1 - p\left(A_t \mid B_t\right) \equiv 1 - p\left(A_t \uparrow B_t\right) \end{aligned} \tag{52}$$

while $p\left(A_t \cap B_t\right)$ is the joint probability of the events A_t and B_t at a same Bernoulli trial t, $p\left(A_t\right)$ is the probability of an event A_t at a same Bernoulli trial t, and $p\left(B_t\right)$ is the probability of an event B_t at a same Bernoulli trial t.

2.1.8. Dependence

Definition 2.12 (**Dependence**).

The dependence of events (Barukčić, 1989, p. 57-61) is defined as

$$p\left(\underbrace{A_t \wedge B_t \wedge C_t \wedge \ldots}_{n \text{ random variables}}\right) \equiv \sqrt[n]{\underbrace{p\left(A_t\right) \times p\left(B_t\right) \times p\left(C_t\right) \times \ldots}_{n \text{ random variables}}} \tag{53}$$

2.1.9. Odds ratio (OR)

Definition 2.13 (Odds ratio (OR))**.**

Odds ratio [16] , [17] have become widely used in medical reports, especially of case-control studies. Odds ratio(Fisher, 1935, p. 50) is defined(Cox, 1958) as the ratio of the odds of an event occurring in one group with respect to the odds of its occurring in another group. Odds(Yule and Pearson, 1900, p. 273) ratio (OR) is a measure of association which quantifies the relationship between two binomial distributed random variables (exposure vs. outcome) and is widely used as an appropriate measure for estimating the relative risk (RR). OR is related (Yule and Pearson, 1900, p. 273) to Yule's (Yule and Pearson, 1900, p. 272) Q(Yule, 1912, p. 585/586). Two events A_t and B_t are regarded as independent if $(A_t, B_t) = 1$. Let

a_t = number of persons exposed to A_t and with disease B_t

b_t = number of persons exposed to A_t but without disease $\underline{B}_t$

c_t = number of persons unexposed $\underline{A}_t$ but with disease B_t

d_t = number of persons unexposed $\underline{A}_t$: and without disease $\underline{B}_t$

a_t+c_t = total number of persons with disease B_t (case-patients)

b_t+d_t = total number of persons without disease $\underline{B}_t$ (controls).

Hereafter, consider the table 3. The odds' ratio (OR) is defined as

Table 3. The two by two table of random variables

		Conditioned/Outcome B_t		
		TRUE	FALSE	
Condition/Exposure	TRUE	a_t	b_t	A_t
A_t	FALSE	c_t	d_t	$\underline{A}_t$
		B_t	$\underline{B}_t$	N_t

$$\begin{aligned} OR(A_t, B_t) &\equiv \left(\frac{a_t}{b_t}\right) / \left(\frac{c_t}{d_t}\right) \\ &\equiv \left(\frac{a_t \times d_t}{b_t \times c_t}\right) \end{aligned} \tag{54}$$

[16] Fisher, R. A. (1935). The Logic of Inductive Inference. Journal of the Royal Statistical Society, 98(1), 39–82.

[17] Cox, D. R. (1958). The Regression Analysis of Binary Sequences. Journal of the Royal Statistical Society. Series B (Methodological), 20(2), 215–242.

Unfortunately, the very high rate of non-replication of research discoveries (lack of confirmation) especially in medical sciences forces us to question several aspects of scientific research. Often, research findings depend too much on financial and other interests, on the peer-review system or prejudices in a scientific field, very great flexibility in study design, erroneous definitions, the use of insufficient statistical methods et cetera and are produced when they should not be produced. Thus, it is hardly surprising that there is increasing evidence that the majority or even the vast majority of currently published research claims are more or less false.[18] , [19] , [20] , [21] , [22] , [23] Hence, we were horrified to realize that today's peer review system based acceptance of publications [24] , [25] has led to a situation in which the majority of peer-review published biomedical research is primarily restricting itself to confirm prevailing bias. Even if the dose makes the poison, today's peer review system constitutes a massive risk to the freedom of science, and it is almost a textbook example of scientific censoring and how not to do things. Odds ratio is such an insufficient statistical method and can support logical fallacies and cause difficulties in drawing logically consistent conclusions. The chorus of voices is growing, which demand the immediate ending(Knol, 2012, Sackett, DL and Deeks, JJ and Altman, DG, 1996) of any use of Odds ratio. Under conditions where (b = 0), the measure of association odds ratio will collapse, because we need to divide by zero, as can be seen at eq. 54. However, according to today's rules of mathematics, a division by zero is neither allowed nor generally accepted as possible. It does no harm to remind ourselves that in the case b = 0 the event A_t is a sufficient condition of B_t. In other words, odds ratio is not able to recognize elementary relationships of objective reality. In fact, it would be a failure not to recognize how dangerous and less valuable odds ratio is. Under conditions where (c = 0) odds ratio collapses too, because we need again to divide by zero, as can be seen at eq. 54. However, and again, today's rules of mathematics don't allow us a division by zero. In point of fact, in the case c = 0 it is more than necessary to point out that A_t is a necessary condition of B_t. In other words, odds ratio or the cross-product ratio is not able to recognize elementary relationships of nature like necessary conditions. We can and need to overcome all the epistemological obstacles as backed by odds ratio entirety. Sooner rather than later, we should give up this measure of relationship completely. Nonetheless, several independent teams addressing the same sets of research questions, should achieve the same research results.

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[19] Ioannidis JP, Haidich AB, Lau J. Any casualties in the clash of randomised and observational evidence? BMJ. 2001 Apr 14;322(7291):879-80. doi: 10.1136/bmj.322.7291.879. PMID: 11302887; PMCID: PMC1120057.

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[21] Sterne JA, Davey Smith G. Sifting the evidence-what's wrong with significance tests? BMJ. 2001 Jan 27;322(7280):226-31. doi: 10.1136/bmj.322.7280.226. PMID: 11159626; PMCID: PMC1119478.

[22] Topol EJ. Failing the public health–rofecoxib, Merck, and the FDA. N Engl J Med. 2004 Oct 21;351(17):1707-9. doi: 10.1056/NEJMp048286. Epub 2004 Oct 6. PMID: 15470193.

[23] Taubes G. Epidemiology faces its limits. Science. 1995 Jul 14;269(5221):164-9. doi: 10.1126/science.7618077. PMID: 7618077.

[24] Le Sueur H, Dagliati A, Buchan I, Whetton AD, Martin GP, Dornan T, Geifman N. Pride and prejudice - What can we learn from peer review? Med Teach. 2020 Sep;42(9):1012-1018. doi: 10.1080/0142159X.2020.1774527. Epub 2020 Jul 6. PMID: 32631121; PMCID: PMC7497287.

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2.1.10. Relative risk (RR)

Relative risk (RR_{nc})

Definition 2.14 (Relative risk (RR_{nc}))**.**

The degree of association between the two binomial variables can be assessed by a number of very different coefficients, the relative (Cornfield, 1951, Sadowsky et al., 1953) risk is one (see Barukčić, 2021c) of them. In general, the original relative risk [26] , [27] RR_{nc}, which approximates to some extent a necessary condition (see Barukčić, 2021c), is defined as

$$\begin{aligned} RR(A_t,B_t)_{nc} &\equiv \frac{\frac{p(a_t)}{p(A_t)}}{\frac{p(c_t)}{p(NotA_t)}} \\ &\equiv \frac{p(a_t)\times p(NotA_t)}{p(c_t)\times p(A_t)} \\ &\equiv \frac{N\times p(a_t)\times N\times p(NotA_t)}{N\times p(c_t)\times N\times p(A_t)} \\ &\equiv \frac{a_t\times (NotA_t)}{c_t\times A_t} \\ &\equiv \frac{EER\,(A_t,B_t)}{CER\,(A_t,B_t)} \end{aligned} \tag{55}$$

That what scientist generally understand by relative risk is the ratio of a probability of an event occurring with an exposure versus the probability of an event occurring without an exposure. In other words,

relative risk = (probability(event in exposed group)) / (probability(the same event in not exposed group)).

A $RR(A_t,B_t) = +1$ means that exposure does not affect the outcome or both are independent of each other while $RR(A_t,B_t)$ less than +1 means that the risk of the outcome is decreased by the exposure. In this context, an $RR(A_t,B_t)$ greater than +1 denotes that the risk of the outcome is increased by the exposure. Widely known problems with odds ratio and relative risk are already documented in literature.

[26] Cornfield J. A method of estimating comparative rates from clinical data; applications to cancer of the lung, breast, and cervix. J Natl Cancer Inst. 1951 Jun;11(6):1269-75. PMID: 14861651.

[27] SADOWSKY DA, GILLIAM AG, CORNFIELD J. The statistical association between smoking and carcinoma of the lung. J Natl Cancer Inst. 1953 Apr;13(5):1237-58. PMID: 13035448.

Relative risk (RR (sc))

Definition 2.15 (Relative risk (RR (sc)))**.**

The relative risk (sc), which provides some evidence of a sufficient (see Barukčić, 2021c) condition, is calculated from the point of view of an outcome and is defined as

$$\begin{aligned} RR(A_t,B_t)_{sc} &\equiv \frac{\frac{p(a_t)}{p(B_t)}}{\frac{p(b_t)}{p(NotB_t)}} \\ &\equiv \frac{p(a_t)\times p(NotB_t)}{p(b_t)\times p(B_t)} \\ &\equiv \frac{N\times p(a_t)\times N\times p(NotB_t)}{N\times p(b_t)\times N\times p(B_t)} \\ &\equiv \frac{a_t\times (NotB_t)}{b_t\times B_t} \\ &\equiv \frac{OPR\,(A_t,B_t)}{CPR\,(A_t,B_t)} \end{aligned} \tag{56}$$

Relative risk reduction (RRR)

Definition 2.16 (Relative risk reduction (RRR))**.**

$$\begin{aligned} RRR\,(A_t,B_t) &\equiv \frac{CER\,(A_t,B_t)-EER\,(A_t,B_t)}{CER\,(A_t,B_t)} \\ &= 1-RR(A_t,B_t) \end{aligned} \tag{57}$$

Vaccine efficacy (VE)

Definition 2.17 (Vaccine efficacy (VE))**.**

Vaccine efficacy is defined as the percentage reduction of a disease in a vaccinated group of people as compared to an unvaccinated group of people.

$$\begin{aligned} VE\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) &\equiv 100 \times\left(1-RR\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right)\right) \\ &\equiv 100 \times\left(\frac{CER\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right)-EER\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right)}{CER\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right)}\right) \end{aligned} \tag{58}$$

Historically, vaccine efficacy has been designed to evaluate the efficacy of a certain vaccine by Greenwood and Yule in 1915 for the cholera and typhoid vaccines(Greenwood and Yule, 1915) and best measured using double-blind, randomized, clinical controlled trials. However, the calculated vaccine efficacy is depending too much on the study design, can lead to erroneous conclusions and is only of very limited value.

Experimental event rate (EER)

Definition 2.18 (Experimental event rate (EER))**.**

$$EER\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) \equiv \frac{p\left(a_{\mathrm{t}}\right)}{p\left(A_{\mathrm{t}}\right)}=\frac{a_{\mathrm{t}}}{a_{\mathrm{t}}+b_{\mathrm{t}}} \tag{59}$$

Definition 2.19 (Control event rate (CER))**.**

$$CER\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) \equiv \frac{p\left(c_{\mathrm{t}}\right)}{p\left(\underline{A}_{\mathrm{t}}\right)}=\frac{c_{\mathrm{t}}}{c_{\mathrm{t}}+d_{\mathrm{t}}} \tag{60}$$

Absolute risk reduction (ARR)

Definition 2.20 (Absolute risk reducation (ARR))**.**

$$\begin{aligned} ARR\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) &\equiv \frac{p\left(c_{\mathrm{t}}\right)}{p\left(\underline{A}_{\mathrm{t}}\right)}-\frac{p\left(a_{\mathrm{t}}\right)}{p\left(A_{\mathrm{t}}\right)} \\ &=\frac{c_{\mathrm{t}}}{c_{\mathrm{t}}+d_{\mathrm{t}}}-\frac{a_{\mathrm{t}}}{a_{\mathrm{t}}+b_{\mathrm{t}}} \\ &=CER\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right)-EER\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) \end{aligned} \tag{61}$$

Absolute risk increase (ARI)

Definition 2.21 (Absolute risk increase (ARI))**.**

$$\begin{aligned} ARI\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) &\equiv \frac{p(a_{\mathrm{t}})}{p(A_{\mathrm{t}})} - \frac{p(c_{\mathrm{t}})}{p(\underline{A}_{\mathrm{t}})} \\ &= EER\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) - CER\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) \end{aligned} \tag{62}$$

Number needed to treat (NNT)

Definition 2.22 (Number needed to treat (NNT))**.**

$$NNT\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) \equiv \frac{1}{CER\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) - EER\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right)} \tag{63}$$

An ideal number needed to treat(Cook and Sackett, 1995, Laupacis et al., 1988), mathematically the reciprocal of the absolute risk reduction, is NNT = 1. Under these circumstances, everyone improves with a treatment, while no one improves with control. A higher number needed to treat indicates more or less a treatment which is less effective.

Number needed to harm (NNH)

Definition 2.23 (Number needed to harm (NNH))**.**

$$NNH\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) \equiv \frac{1}{EER\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) - CER\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right)} \tag{64}$$

The number needed to harm (Massel and Cruickshank, 2002), mathematically the inverse of the absolute risk increase, indicates at the end how many patients need to be exposed to a certain factor, in order to observe a harm in one patient that would not otherwise have been harmed.

Outcome prevalence rate (OPR)

Definition 2.24 (Outcome prevalence rate (OPR))**.**

$$OPR\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) \equiv \frac{p(a_{\mathrm{t}})}{p(B_{\mathrm{t}})} = \frac{a_{\mathrm{t}}}{a_{\mathrm{t}} + c_{\mathrm{t}}} \tag{65}$$

Control prevalence rate (CPR)

Definition 2.25 (Control prevalence rate (CPR))**.**

$$CPR\,(A_{\mathrm{t}},B_{\mathrm{t}}) \equiv \frac{p(b_{\mathrm{t}})}{p(\underline{B}_{\mathrm{t}})} = \frac{b_{\mathrm{t}}}{b_{\mathrm{t}}+d_{\mathrm{t}}} \tag{66}$$

Bias and confounding is present to some degree in all research. In order to assess the relationship of exposure with a disease or an outcome, a fictive control group (i.e. of newborn or of young children et cetera) can be of use too. Under certain circumstances, even a CPR = 0 is imaginable.

Absolute prevalence reduction (APR)

Definition 2.26 (Absolute prevalence reduction (APR))**.**

$$APR\,(A_{\mathrm{t}},B_{\mathrm{t}}) \equiv CPR\,(A_{\mathrm{t}},B_{\mathrm{t}}) - OPR\,(A_{\mathrm{t}},B_{\mathrm{t}}) \tag{67}$$

Absolute prevalence increase (API)

Definition 2.27 (Absolute prevalence increase (API))**.**

$$API\,(A_{\mathrm{t}},B_{\mathrm{t}}) \equiv OPR\,(A_{\mathrm{t}},B_{\mathrm{t}}) - CPR\,(A_{\mathrm{t}},B_{\mathrm{t}}) \tag{68}$$

Relative prevalence reduction (RPR)

Definition 2.28 (Relative prevalence reduction (RPR))**.**

$$\begin{aligned} RPR\,(A_{\mathrm{t}},B_{\mathrm{t}}) &\equiv \frac{CPR\,(A_{\mathrm{t}},B_{\mathrm{t}}) - OPR\,(A_{\mathrm{t}},B_{\mathrm{t}})}{CPR\,(A_{\mathrm{t}},B_{\mathrm{t}})} \\ &= 1 - RR(A_{\mathrm{t}},B_{\mathrm{t}})_{\mathrm{sc}} \end{aligned} \tag{69}$$

The index NNS

Definition 2.29 (The index NNS)**.**

$$NNS\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)\equiv\frac{1}{CPR\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)-OPR\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)} \tag{70}$$

Mathematically, the index NNS is the reciprocal of the absolute prevalence reduction.

The index NNI

Definition 2.30 (The index NNI)**.**

$$NNI\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)\equiv\frac{1}{OPR\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)-CPR\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)} \tag{71}$$

Mathematically, the index NNI is the reciprocal of the absolute prevalence increase.

2.1.11. Study design and bias

Systematic observation and experimentation, inductive and deductive reasoning are essential for any formation and testing of hypotheses and theories about the natural world. In one way or another, logically and mathematically sound scientific methods and concepts are crucial constituents of any scientific progress. When all goes well, different scientists at different times and places using the same scientific methodology should be able to generate the same scientific knowledge. However, more than half (52%) of scientists surveyed believe that studies do not successfully reproduce sufficiently similar or the same results as the original studies (Baker, 2016). In a very large study on publication bias in meta-analyses, Kicinski et al. (Kicinski et al., 2015) found evidence of publication bias even in systematic reviews. Therefore, a careful re-evaluation of the study/experimental design, the statistical methods and other scientific means which underpin scientific inquiry and research goals appears to be necessary once and again. While it is important to recognize the shortcoming of today's science, one issue which has shaped debates over studies published is the question: **has a study really measured what it set out to**? Even if studies carried out can vary greatly in detail, the data from the studies itself provide information about the credibility of the data.

Index of unfairness (IOU)

Definition 2.31 (**Index of unfairness**)**.**

The index of unfairness (Barukčić, 2019b) (IOU) is defined as

$$p\left(IOU\left(A,B\right)\right) \equiv Absolute\left(\left(\frac{A+B}{N}\right)-1\right) \tag{72}$$

A very good study design should assure as much as possible a p(IOU) = 0. In point of fact, against the background of lacking enough experience with the use of p(IOU), a p(IOU) up to 0.25 could be of use too. An index of unfairness is of use to prove whether sample data are biased and whether sample data can be used for Chi-square based analysis of necessary conditions, of sufficient conditions and of causal relationships.

Index of independence (IOI)

Definition 2.32 (**Index of independence**)**.**

The index of independence(Barukčić, 2019a) (IOI) is defined as

$$p\left(IOI\left(A_t,\underline{B}_t\right)\right) \equiv Absolute\left(\left(\frac{A_t+\underline{B}_t}{N}\right)-1\right) \tag{73}$$

or as

$$p\left(IOI\left(\underline{A}_t,B_t\right)\right) \equiv Absolute\left(\left(\frac{\underline{A}_t+B_t}{N}\right)-1\right) \tag{74}$$

A very good study design which aims to prove **an exclusion relationship or a causal relationship** should assure as much as possible a p(IOI) = 0. However, once again, against the background of lacking enough experience with the use of p(IOI), sample data with a p(IOI) up to 0.25 are of use too. Today, most double-blind placebo-controlled studies are based on the demand that **p(IOU) = p(IOI)** while the value of p(IOU) of has been widely neglected. Such an approach leads to unnecessary big sample sizes, the increase of cost, the waste of time and, most importantly of all, to epistemological systematically biased sample data and conclusions drawn. A change is necessary.

Index of relationship (IOR)

Definition 2.33 (Index of relationship (IOR))**.**

Due to several reasons, it is not always easy to identify the unique characteristics between two events like A_t and B_t. And more than that, it is difficult to decide what to do, and much more difficult to know in which direction one should think and which decision is right. Sometimes it is helpful to know at least something about the direction of the relationship between two events like A_t and B_t. Under conditions where $p(a_t) = p(A_t \wedge B_t)$, the index of relationship(Barukčić, 2021b), abbreviated as IOR, is defined as

$$
\begin{aligned}
IOR(A_t, B_t) &\equiv \left(\frac{p(A_t \wedge B_t)}{p(B_t) \times p(A_t)} \right) - 1 \\
&\equiv \left(\frac{p(a_t)}{p(B_t) \times p(A_t)} \right) - 1 \\
&\equiv \left(\left(\frac{N \times N \times p(a_t)}{N \times p(B_t) \times N \times p(A_t)} \right) - 1 \right) \\
&\equiv \left(\left(\frac{N \times a}{A \times B} \right) - 1 \right)
\end{aligned}
\tag{75}
$$

where $p(A_t)$ denotes the probability of an event A_t at the Bernoulli trial t and $p(B_t)$ denotes the probability of another event B_t at the same Bernoulli trial t while $p(a_t)$ denotes the joint probability of $p(A_t$ AND $B_t)$ at the same Bernoulli trial t and a, A and B may denote the expectation values.

2.2. Conditions

2.2.1. Exclusion relationship

Definition 2.34 (**Exclusion relationship [*EXCL*]**).

Mathematically, the exclusion (EXCL) relationship, denoted by $p(A_t \mid B_t)$ in terms of statistics and probability theory, is defined(Barukčić, 1989, p. 68-70) as

$$\begin{aligned} p(A_t \mid B_t) &\equiv p(A_t \uparrow B_t) \\ &\equiv p(b_t) + p(c_t) + p(d_t) \\ &\equiv \frac{N \times (p(b_t) + p(c_t) + p(d_t))}{N} \\ &\equiv \frac{\sum_{t=1}^{N} (\underline{A}_t \vee \underline{B}_t)}{N} \equiv \frac{b+c+d}{N} \\ &\equiv \frac{b+\underline{A}}{N} \\ &\equiv \frac{c+\underline{B}}{N} \\ &\equiv +1 \end{aligned} \tag{76}$$

Based on the 1913 Henry Maurice Sheffer (1882-1964) relationship, the Sheffer stroke(Nicod, 1917, Sheffer, 1913) usually denoted by $\uparrow$, it is $p(A_t \wedge B_t) \equiv 1 - p(A_t \mid B_t)$ (see table 4).

Table 4. A_t excludes B_t and vice versa.

		Conditioned (COVID-19) B_t		
		TRUE	FALSE	
Condition (Vaccine)	TRUE	**+0**	$p(b_t)$	$p(A_t)$
A_t	FALSE	$p(c_t)$	$p(d_t)$	$p(\underline{A}_t)$
		$p(B_t)$	$p(\underline{B}_t)$	+1

Example 2.1. *Pfizer Inc. and BioNTech SE announced on Monday, November 09, 2020 - 06:45am results from a Phase 3 COVID-19 vaccine trial with 43.538 participants which provides evidence that their vaccine (BNT162b2) is preventing COVID-19 in participants without evidence of prior SARS-CoV-2 infection. In toto, 170 confirmed cases of COVID-19 were evaluated, with 8 in the vaccine group versus 162 in the placebo group. The exclusion relationship can be calculated as follows.*

$$\begin{aligned} p(Vaccine : BNT162b2 \mid COVID-19(infection)) &\equiv p(b_t) + p(c_t) + p(d_t) \\ &\equiv 1 - p(a_t) \\ &\equiv 1 - \left(\frac{8}{43538}\right) \\ &\equiv +0,99981625 \end{aligned} \tag{77}$$

with a P Value = 0,000184.

Following Kolmogorov's definition of an n-dimensional probability density (see also Kolmogorov, Andreĭ Nikolaevich, 1950, p. 26) of random variables A_t, B_t et cetera at the point t, we obtain

$$\begin{aligned} p\left(A_t \mid B_t\right) &\equiv p\left(\underline{U}_t \cup \underline{W}_t\right) \\ &\equiv 1 - p\left(A_t \cap B_t\right) \\ &\equiv 1 - \int_{-\infty}^{A_t} \int_{-\infty}^{B_t} f\left(A_t, B_t\right)\, dA_t\, dB_t \\ &\equiv +1 \end{aligned} \tag{78}$$

while $p\left(A_t \mid B_t\right)$ would denote the cumulative distribution function of random variables and $f\left(A_t, B_t\right)$ is the joint density function.

2.2.2. Observational study and exclusion relationship

Under conditions of an observational study, the exclusion relationship follows approximately(see Barukčić, 2021a) as

$$p\left(A_t \mid B_t\right) \equiv p\left(A_t \uparrow B_t\right) \geq 1 - \frac{p\left(a_t\right)}{p\left(B_t\right)} \tag{79}$$

2.2.3. Experimental study and exclusion relationship

Under conditions of an experimental study, the exclusion relationship follows approximately(see Barukčić, 2021a) as

$$p\left(A_t \mid B_t\right) \equiv p\left(A_t \uparrow B_t\right) \geq 1 - \frac{p\left(a_t\right)}{p\left(A_t\right)} \tag{80}$$

2.2.4. The goodness of fit test of an exclusion relationship

Definition 2.35 (The $\tilde{\chi}^2$ goodness of fit test of an exclusion relationship).

Under some well known circumstances, testing hypothesis about an exclusion relationship $p(A_t \mid B_t)$ is possible by the chi-square distribution (also chi-squared or $\tilde{\chi}^2$-distribution) too. The $\tilde{\chi}^2$ goodness of fit test of an exclusion relationship with degree of freedom (d. f.) of d. f. = 1 is calculated as

$$\begin{aligned}\tilde{\chi}^2{}_{\text{Calculated}}\left((A_{\text{t}} \mid B_{\text{t}}) \mid A\right) &\equiv \frac{(b-(a+b))^2}{A}+ \\ &\quad \frac{((c+d)-\underline{A})^2}{\underline{A}} \\ &\equiv \frac{a^2}{A}+0 \\ &\equiv \frac{a^2}{A}\end{aligned} \tag{81}$$

or equally as

$$\begin{aligned}\tilde{\chi}^2{}_{\text{Calculated}}\left((A_{\text{t}} \mid B_{\text{t}}) \mid B\right) &\equiv \frac{(c-(a+c))^2}{B}+ \\ &\quad \frac{((b+d)-\underline{B})^2}{\underline{B}} \\ &\equiv \frac{a^2}{B}+0 \\ &\equiv \frac{a^2}{B}\end{aligned} \tag{82}$$

and can be compared with a theoretical chi-square value at a certain level of significance α. The $\tilde{\chi}^2$-distribution equals zero when the observed values are equal to the expected/theoretical values of an exclusion relationship/distribution $\text{p}(\text{A}_{\text{t}} \mid \text{B}_{\text{t}})$, in which case the null hypothesis has to be accepted. Yate's (Yates, 1934) continuity correction was not used under these circumstances.

2.2.5. The left-tailed p Value of an exclusion relationship

Definition 2.36 (**The left-tailed p Value of an exclusion relationship**).

It is known that as a sample size, N, increases, a sampling distribution of a special test statistic approaches the normal distribution (central limit theorem). Under these circumstances, the left-tailed (lt) p Value (Barukčić, 2019c) of an exclusion relationship can be calculated as follows.

$$\begin{aligned}pValue_{\text{lt}}\left(A_{\text{t}} \mid B_{\text{t}}\right) &\equiv 1-e^{-(1-p(A_{\text{t}}|B_{\text{t}}))} \\ &\equiv 1-e^{-(a/N)}\end{aligned} \tag{83}$$

A low p-value may provide some evidence of statistical significance.

2.2.6. Neither nor conditions

Definition 2.37 (**Neither A_{t} nor B_{t} conditions [*NOR*]**).

Mathematically, a neither A_t nor B_t condition (or rejection according to the French philosopher and logician Jean George Pierre Nicod (1893-1924), i.e. Jean Nicod's statement (Nicod, 1924)) relationship (NOR), denoted by $p(A_t \downarrow B_t)$ in terms of statistics and probability theory, is defined (Barukčić, 1989, p. 68-70) as

$$\begin{aligned} p\left(A_t \downarrow B_t\right) &\equiv p\left(d_t\right) \\ &\equiv \frac{N - \sum_{t=1}^{N} \left(A_t \vee B_t\right)}{N} \equiv \frac{\sum_{t=1}^{N} \left(\underline{A}_t \wedge \underline{B}_t\right)}{N} \equiv \frac{N \times \left(p\left(d_t\right)\right)}{N} \\ &\equiv \frac{d}{N} \\ &\equiv +1 \end{aligned} \tag{84}$$

2.2.7. The Chi square goodness of fit test of a neither nor condition relationship

Definition 2.38 (The $\tilde{\chi}^2$ goodness of fit test of a neither A_t nor B_t condition relationship).

A neither A_t nor B_t condition relationship $p(A_t \downarrow B_t)$ can be tested by the chi-square distribution (also chi-squared or $\tilde{\chi}^2$-distribution). The $\tilde{\chi}^2$ goodness of fit test of a neither A_t nor B_t condition relationship with degree of freedom (d. f.) of d. f. = 1 may be calculated as

$$\begin{aligned} {\tilde{\chi}^2}_{\text{Calculated}}\left(\left(A_t \downarrow B_t\right) \mid A\right) &\equiv \frac{\left(d - \left(c + d\right)\right)^2}{\underline{A}} + \\ &\quad \frac{\left(\left(a + b\right) - A\right)^2}{A} \\ &\equiv \frac{c^2}{\underline{A}} + 0 \end{aligned} \tag{85}$$

or equally as

$$\begin{aligned} {\tilde{\chi}^2}_{\text{Calculated}}\left(\left(A_t \downarrow B_t\right) \mid B\right) &\equiv \frac{\left(d - \left(b + d\right)\right)^2}{\underline{B}} + \\ &\quad \frac{\left(\left(a + c\right) - B\right)^2}{B} \\ &\equiv \frac{b^2}{\underline{B}} + 0 \end{aligned} \tag{86}$$

Yate's (Yates, 1934) continuity correction has not been used in this context.

2.2.8. The left-tailed p Value of a neither nor B condition relationship

Definition 2.39 (The left-tailed p Value of a neither A_t nor B_t condition relationship).

The left-tailed (lt) p Value (Barukčić, 2019c) of a neither A_t nor B_t condition relationship can be calculated as follows.

$$\begin{aligned} pValue_{\text{lt}}\left(A_t \downarrow B_t\right) &\equiv 1 - e^{-(1-p(A_t \downarrow B_t))} \\ &\equiv 1 - e^{-p(A_t \vee B_t)} \\ &\equiv 1 - e^{-((a+b+c)/N)} \end{aligned} \tag{87}$$

where $\vee$ may denote disjunction or logical inclusive or. In this context, a low p-value indicates again a statistical significance. In general, it is $p\left(A_t \vee B_t\right) \equiv 1 - p\left(A_t \downarrow B_t\right)$ (see table 5).

Table 5. Neither A_t nor B_t relationship.

		Conditioned B_t		
		YES	NO	
Condition A_t	YES	0	0	0
	NO	0	1	1
		0	1	1

2.2.9. Necessary condition

Definition 2.40 (**Necessary condition [*Conditio sine qua non*]**).

Despite the most extended efforts, the current state of research on conditions and conditioned is still incomplete and very contradictory. However, even thousands of years ago and independently of any human mind and consciousness, water has been and is still a necessary condition for (human) life. Without water, there has been and there is no (human) life. It comes therefore as no surprise that one of the first documented attempts to present a rigorous theory of conditions and causation (see also Aristotle et al., 1908, Metaphysica III 2 997a 10 and 13/14) came from the Greek philosopher and scientist Aristotle (384-322 BCE). Thus far, it is amazing that Aristotle himself made already a strict distinction between conditions and causes. Taking Aristotle very seriously, it is necessary to consider that

> "... everything which has a ... ... potency in question ... ... has the potency ... of acting ...
>
> not in all circumstances but on certain conditions ... "
>
> (see also Aristotle et al., 1908, Metaphysica IX 5 1048a 14-19)

Before going into details, Aristotle went on to define the necessary condition as follows.

"... necessary ... means ...

without ... a condition, a thing cannot live ... "

(see also Aristotle et al., 1908, Metaphysica V 2 1015a 20-22)

In point of fact, Aristotle developed a theory of conditions and causality commonly referred to as the doctrine of four causes. Many aspects and general features of Aristotle's logical concept of causality are meanwhile extensively and critically debated in secondary literature. However, even if the Greek philosophers Heraclitus, Plato, Aristotle et cetera numbers among the greatest philosophers of all time, the philosophy has evolved. Scientific knowledge and objective reality are deeply interrelated and cannot be reduced only to Greek philosophers like Aristotle. As mentioned at the start of the article, the specification of necessary conditions has traditionally been part of the philosopher's investigations of different phenomena. Behind the need of a detailed evidence, it is justified to consider that philosophy or philosophers as such certainly do not possess **a monopoly on the truth** and other areas such as medicine as well as other sciences and technology may transmit truths as well and may be of help to move beyond one's self enclosed unit. Seemingly, **the law's concept of causation** justifies to say few words on this subject, to put some light on some questions. Are there any criteria in law for deciding whether one action or an event A_t has caused another (generally harmful) event B_t? What are these criteria? May causation in legal contexts differ from causation outside the law, for example, in science or in our everyday life and to what extent? Under which circumstances is it justified to tolerate such differences as may be found to exist? To understand just what is the law's concept of causation, it is useful to know how the highest court of states is dealing with causation. In the case *Hayes v. Michigan Central R. Co., 111 U.S. 228*, the U.S. Supreme Court defined 1884 conditio sine qua non as follows: "... **causa sine qua non – a cause which, if it had not existed, the injury would not have taken place**". (Justice Matthews, Mr., 1884) The German Bundesgerichtshof für Strafsachen stressed once again the importance of conditio sine qua non relationship in his decision by defining the following: "**Ursache eines strafrechtlich bedeutsamen Erfolges jede Bedingung, die nicht hinweggedacht werden kann, ohne daß der Erfolg entfiele**"(Bundesgerichtshof für Strafsachen, 1951) Another lawyer elaborated on the basic issue of **identity and difference between cause and condition**. Von Bar was writing: "Die erste Voraussetzung, welche erforderlich ist, damit eine Erscheinung als die Ursache einer anderen bezeichnet werden könne, ist, daß jene eine der Bedingungen dieser sein. Würde die zweite Erscheinung auch dann eingetreten sein, wenn die erste nicht vorhanden war, so ist sie in keinem Falle Bedingung und noch weniger Ursache. Wo immer ein Kausalzusammenhang behauptet wird, da muß er wenigstens diese Probe aushalten ... **Jede Ursache ist nothwendig auch eine Bedingung eines Ereignisses; aber nicht jede Bedingung ist Ursache zu nennen**."(Bar, 1871) Von Bar's position translated into English: *The first requirement, which is required, thus that something could be called as the cause of another, is that the one has to be one of the conditions of the other. If the second something had occurred even if the first one did not exist, so it is by no means a condition and still less a cause. Wherever a causal relationship is claimed, the same must at least withstand this test... Every cause is necessarily also a condition of an event too; but not every condition is cause*

too. Thus far, let us consider among other the following in order to specify necessary conditions from another, probabilistic point of view. An event (i.e. A_t) which is a necessary condition of another event or outcome (i.e. B_t) must be given, must be present for a conditioned, for an event or for an outcome B_t to occur. A necessary condition (i.e. A_t) is a requirement which must be fulfilled **at every single Bernoulli trial t**, in order for a conditioned or an outcome (i.e. B_t) to occur, but it alone does not determine the occurrence of an event. In other words, if a necessary condition (i.e. A_t) is given, an outcome (i.e. B_t) need not occur. In contrast to a necessary condition, a 'sufficient'condition is the one condition which 'guarantees'that an outcome will take place or must occur for sure. Under which conditions we may infer about the unobserved and whether observations made are able at all to justify predictions about potential observations which have not yet been made or even general claims which my go even beyond the observed (*the 'problem of induction')* is not the issue of the discussion at this point. Besides of the principal necessity of meeting such a challenge, a necessary condition of an event can but need not be at the same Bernoulli trial t a sufficient condition for an event to occur. However, theoretically, it is possible that an event or an outcome is determined by many necessary conditions. Let us focus to some extent on what this means, or in other words how much importance can we attribute to such a special case. *Example*. A human being cannot live without oxygen. A human being cannot live without water. A human being cannot live without a brain. A human being cannot live without kidneys. A human being cannot live without ... et cetera. Thus far, even if oxygen is given, if water is given, if a brain is given, without functioning kidney's (or something similar) a human being will not survive on the long run. This example is of use to reach the following conclusion. Although it might seem somewhat paradoxical at first sight, **even under circumstances where a condition or an outcome depends on several different necessary conditions it is particularly important that every single of these necessary conditions for itself must be given otherwise the conditioned (i.e. the outcome) will not occur**. Mathematically, the necessary condition (SINE) relationship, denoted by $p(A_t \leftarrow B_t)$ in terms of statistics and probability theory, is defined (Barukčić, 1989, p. 15-28) as

$$\begin{aligned} p\left(A_t \leftarrow B_t\right) \equiv p\left(A_t \vee \underline{B}_t\right) &\equiv \frac{\sum_{t=1}^{N}\left(A_t \vee \underline{B}_t\right)}{N} \equiv \frac{\left(A_t \vee \underline{B}_t\right) \times p\left(A_t \vee \underline{B}_t\right)}{\left(A_t \vee \underline{B}_t\right)} \\ &\equiv p\left(a_t\right) + p\left(b_t\right) + p\left(d_t\right) \\ &\equiv \frac{N \times \left(p\left(a_t\right) + p\left(b_t\right) + p\left(d_t\right)\right)}{N} \equiv \frac{E\left(A_t \leftarrow B_t\right)}{N} \\ &\equiv \frac{a+b+d}{N} \equiv \frac{E\left(A_t \vee \underline{B}_t\right)}{N} \\ &\equiv \frac{A+d}{N} \equiv \frac{E\left(A_t \leftarrow B_t\right)}{N} \\ &\equiv \frac{a+\underline{B}}{N} \equiv \frac{E\left(A_t \vee \underline{B}_t\right)}{N} \\ &\equiv +1 \end{aligned} \tag{88}$$

where $E\left(A_t \leftarrow B_t\right) \equiv E\left(A_t \vee \underline{B}_t\right)$ indicates the expectation value of the necessary condition. In general, it is $p\left(A_t \prec B_t\right) \equiv 1 - p\left(A_t \leftarrow B_t\right)$ (see Table 6).

Remark 2.1. *A necessary condition A_t is characterized itself by the property that another event B_t will not occur if A_t is not given, if A_t did not occur (Barukčić, 1989, 1997, 2005, 2016b, 2017b,c,*

Table 6. Necessary condition.

		Conditioned B_t		
		TRUE	FALSE	
Condition	TRUE	$p(a_t)$	$p(b_t)$	$p(A_t)$
A_t	FALSE	**+0**	$p(d_t)$	$p(\underline{A}_t)$
		$p(B_t)$	$p(\underline{B}_t)$	+1

*2020a,b,c,d, Barukčić and Ufuoma, 2020). **Example**. Once again, a human being cannot live without water. A human being cannot live without gaseous oxygen, et cetera. Water itself is a necessary condition for human life. However, gaseous oxygen is a necessary condition for human life too. Thus far, even if water is given and even if water is a necessary condition for human life, without gaseous oxygen there will be no human life. In general, if a conditioned or an outcome B_t depends on the necessary condition A_t and equally on numerous other necessary conditions, an event B_t will not occur if A_t itself is not given independently of the occurrence of other necessary conditions.*

Taking into account Kolmogorov's definition of an n-dimensional probability density (see also Kolmogorov, Andreĭ Nikolaevich, 1950, p. 26) of random variables A_t, B_t et cetera at the (period of) time t, we obtain

$$\begin{aligned} p\left(A_t \leftarrow B_t\right) &\equiv +1 \\ &\equiv +1 - p\left(c_t\right) \\ &\equiv +1 - p\left(\underline{A}_t \cap B_t\right) \\ &\equiv \left(\int_{-\infty}^{A_t} \int_{-\infty}^{B_t} f\left(A_t, B_t\right)\, dA_t\, dB_t \right) + \left(1 - \int_{-\infty}^{B_t} f\left(B_t\right)\, dB_t \right) \end{aligned} \tag{89}$$

while $p\left(A_t \leftarrow B_t\right)$ would denote the cumulative distribution function of random variables of a necessary condition. Another adequate formulation of a necessary condition is possible too.

2.2.10. The Chi-square goodness of fit test of a necessary condition relationship

Definition 2.41 (The $\tilde{\chi}^2$ goodness of fit test of a necessary condition relationship).

Under some well known circumstances, hypothesis about the conditio sine qua non relationship $p(A_t \leftarrow B_t)$ can be tested by the chi-square distribution (also chi-squared or χ^2-distribution), first described by the German statistician Friedrich Robert Helmert (Helmert, 1876) and later rediscovered by Karl Pearson (Pearson, 1900) in the context of a goodness of fit test. The $\tilde{\chi}^2$ goodness of fit test of a conditio sine qua non relationship with degree of freedom (d. f.) of d. f. = 1 is calculated as

$$\begin{aligned}\tilde{\chi}^2{}_{\text{Calculated}}\left(A_{\text{t}} \leftarrow B_{\text{t}} \mid B\right) &\equiv \frac{\left(a-(a+c)\right)^2}{B}+ \\ &\quad \frac{\left((b+d)-\underline{B}\right)^2}{\underline{B}} \\ &\equiv \frac{c^2}{B}+0 \\ &\equiv \frac{c^2}{B}\end{aligned} \tag{90}$$

or equally as

$$\begin{aligned}\tilde{\chi}^2{}_{\text{Calculated}}\left(A_{\text{t}} \leftarrow B_{\text{t}} \mid \underline{A}\right) &\equiv \frac{\left(d-(c+d)\right)^2}{\underline{A}}+ \\ &\quad \frac{\left((a+b)-A\right)^2}{A} \\ &\equiv \frac{c^2}{\underline{A}}+0 \\ &\equiv \frac{c^2}{\underline{A}}\end{aligned} \tag{91}$$

and can be compared with a theoretical chi-square value at a certain level of significance α. It has not yet been finally clarified whether the use of Yate's (Yates, 1934) continuity correction is necessary at all.

2.2.11. The left-tailed p Value of the conditio sine qua non relationship

Definition 2.42 (The left-tailed p Value of the conditio sine qua non relationship).

The left-tailed (lt) p Value (Barukčić, 2019c) of the conditio sine qua non relationship can be calculated as follows.

$$\begin{aligned}pValue_{\text{lt}}\left(A_{\text{t}} \leftarrow B_{\text{t}}\right) &\equiv 1-e^{-\left(1-p\left(A_{\text{t}} \leftarrow B_{\text{t}}\right)\right)} \\ &\equiv 1-e^{-(c/N)}\end{aligned} \tag{92}$$

2.2.12. Sufficient condition

Definition 2.43 (Sufficient condition [*Conditio per quam*]).

Mathematically, the sufficient condition (IMP) relationship, denoted by $\mathrm{p}(\mathrm{A_t} \rightarrow \mathrm{B_t})$ in terms of statistics and probability theory, is defined(Barukčić, 1989, p. 68-70) as

$$\begin{aligned} p\left(A_{\mathrm{t}} \rightarrow B_{\mathrm{t}}\right) \equiv p\left(\underline{A}_{\mathrm{t}} \vee B_{\mathrm{t}}\right) &\equiv \frac{\sum_{t=1}^{N}\left(\underline{A}_{\mathrm{t}} \vee B_{\mathrm{t}}\right)}{N} \equiv \frac{\left(\underline{A}_{\mathrm{t}} \vee B_{\mathrm{t}}\right) \times p\left(\underline{A}_{\mathrm{t}} \vee B_{\mathrm{t}}\right)}{\left(\underline{A}_{\mathrm{t}} \vee B_{\mathrm{t}}\right)} \\ &\equiv p\left(a_{\mathrm{t}}\right)+p\left(c_{\mathrm{t}}\right)+p\left(d_{\mathrm{t}}\right) \\ &\frac{N \times\left(p\left(a_{\mathrm{t}}\right)+p\left(c_{\mathrm{t}}\right)+p\left(d_{\mathrm{t}}\right)\right)}{N} \\ &\equiv \frac{a+c+d}{N} \equiv \frac{E\left(\underline{A}_{\mathrm{t}} \vee B_{\mathrm{t}}\right)}{N} \\ &\equiv \frac{B+d}{N} \equiv \frac{E\left(A_{\mathrm{t}} \rightarrow B_{\mathrm{t}}\right)}{N} \\ &\equiv \frac{a+\underline{A}}{N} \\ &\equiv +1 \end{aligned} \tag{93}$$

It is $p\left(A_{\mathrm{t}} \succ\!\!-B_{\mathrm{t}}\right) \equiv 1-p\left(A_{\mathrm{t}} \rightarrow B_{\mathrm{t}}\right)$ (see Table 7).

Table 7. Sufficient condition.

		Conditioned $\mathrm{B_t}$		
		TRUE	FALSE	
Condition	TRUE	$\mathrm{p(a_t)}$	**+0**	$\mathrm{p(A_t)}$
$\mathrm{A_t}$	FALSE	$\mathrm{p(c_t)}$	$\mathrm{p(d_t)}$	$\mathrm{p(\underline{A}_t)}$
		$\mathrm{p(B_t)}$	$\mathrm{p(\underline{B}_t)}$	+1

Remark 2.2. *A sufficient condition A_t is characterized by the property that another event B_t will occur if A_t is given, if A_t itself occured (Barukčić, 1989, 1997, 2005, 2016b, 2017b,c, 2020a,b,c,d, Barukčić and Ufuoma, 2020).* ***Example****. The ground, the streets, the trees, human beings and many other objects too will become wet during heavy rain. Especially,* ***if*** *it is raining (event A_t),* ***then*** *human beings will become wet (event B_t). However, even if this is a common human wisdom, a human being equipped with an appropriate umbrella (denoted by R_t) need not become wet even during heavy rain. An appropriate umbrella (R_t) is similar to an event with the potential to counteract the occurrence of another event (B_t) and can be understood something as an* ***anti-dot*** *of another event. In other words, an appropriate umbrella is an antidote of the effect of rain on human body, an appropriate umbrella has the potential to protect humans from the effect of rain on their body. It is a good rule of thumb that the following relationship*

$$p\left(A_t \rightarrow B_t\right)+p\left(R_t \wedge B_t\right) \equiv +1 \tag{94}$$

indicates that R_t is an antidote of A_t. However, taking a shower, swimming in a lake et cetera may make human hair wet too. More than anything else, however, these events does not affect the final outcome, the effect of raining on human body.

2.2.13. The Chi square goodness of fit test of a sufficient condition relationship

Definition 2.44 (**The $\tilde{\chi}^2$ goodness of fit test of a sufficient condition relationship**).

Under some well known circumstances, testing hypothesis about the conditio per quam relationship $p(A_t \rightarrow B_t)$ is possible by the chi-square distribution (also chi-squared or $\tilde{\chi}^2$-distribution) too. The $\tilde{\chi}^2$ goodness of fit test of a conditio per quam relationship with degree of freedom (d. f.) of d. f. = 1 is calculated as

$$\begin{aligned} \tilde{\chi}^2{}_{\text{Calculated}}\left(A_t \rightarrow B_t \mid A\right) &\equiv \frac{\left(a-(a+b)\right)^2}{A}+ \\ &\quad \frac{\left((c+d)-\underline{A}\right)^2}{\underline{A}} \\ &\equiv \frac{b^2}{A}+0 \\ &\equiv \frac{b^2}{A} \end{aligned} \tag{95}$$

or equally as

$$\begin{aligned} \tilde{\chi}^2{}_{\text{Calculated}}\left(A_t \rightarrow B_t \mid \underline{B}\right) &\equiv \frac{\left(d-(b+d)\right)^2}{\underline{B}}+ \\ &\quad \frac{\left((a+c)-B\right)^2}{B} \\ &\equiv \frac{b^2}{\underline{B}}+0 \\ &\equiv \frac{b^2}{\underline{B}} \end{aligned} \tag{96}$$

and can be compared with a theoretical chi-square value at a certain level of significance α. The $\tilde{\chi}^2$-distribution equals zero when the observed values are equal to the expected/theoretical values of the conditio per quam relationship/distribution $p(A_t \rightarrow B_t)$, in which case the null hypothesis is accepted. Yate's (Yates, 1934) continuity correction has not been used in this context.

2.2.14. The left-tailed p Value of the conditio per quam relationship

Definition 2.45 (**The left-tailed p Value of the conditio per quam relationship**).

The left-tailed (lt) p Value (Barukčić, 2019c) of the conditio per quam relationship can be calculated

as follows.

$$\begin{aligned} pValue_{\mathrm{lt}}\left(A_{\mathrm{t}} \rightarrow B_{\mathrm{t}}\right) &\equiv 1-e^{-(1-p(A_{\mathrm{t}} \rightarrow B_{\mathrm{t}}))} \\ &\equiv 1-e^{-(b/N)} \end{aligned} \tag{97}$$

Again, a low p-value indicates a statistical significance.

2.2.15. Necessary and sufficient conditions

Definition 2.46 (**Necessary and sufficient conditions [*EQV*]**).

The necessary and sufficient condition (EQV) relationship, denoted by $\mathrm{p}(\mathrm{A_t} \leftrightarrow \mathrm{B_t})$ in terms of statistics and probability theory, is defined(Barukčić, 1989, p. 68-70) as

$$\begin{aligned} p\left(A_{\mathrm{t}} \leftrightarrow B_{\mathrm{t}}\right) &\equiv \frac{\sum_{t=1}^{N}\left(\left(A_{\mathrm{t}} \vee \underline{B}_{\mathrm{t}}\right) \wedge \left(\underline{A}_{\mathrm{t}} \vee B_{\mathrm{t}}\right)\right)}{N} \\ &\equiv p\left(a_{\mathrm{t}}\right)+p\left(d_{\mathrm{t}}\right) \\ &\equiv \frac{N \times \left(p\left(a_{\mathrm{t}}\right)+p\left(d_{\mathrm{t}}\right)\right)}{N} \\ &\equiv \frac{a+d}{N} \\ &\equiv +1 \end{aligned} \tag{98}$$

2.2.16. The Chi square goodness of fit test of a necessary and sufficient condition relationship

Definition 2.47 (**The $\tilde{\chi}^2$ goodness of fit test of a necessary and sufficient condition relationship**).

Even the necessary and sufficient condition relationship $\mathrm{p}(\mathrm{A_t} \leftrightarrow \mathrm{B_t})$ can be tested by the chi-square distribution (also chi-squared or $\tilde{\chi}^2$-distribution) too. The $\tilde{\chi}^2$ goodness of fit test of a necessary and sufficient condition relationship with degree of freedom (d. f.) of d. f. = 1 is calculated as

$$\begin{aligned} {\tilde{\chi}^2}_{\mathrm{Calculated}}\left(A_{\mathrm{t}} \leftrightarrow B_{\mathrm{t}} \mid A\right) &\equiv \frac{\left(a-(a+b)\right)^2}{A}+ \\ &\quad \frac{d-\left((c+d)\right)^2}{\underline{A}} \\ &\equiv \frac{b^2}{A}+\frac{c^2}{\underline{A}} \end{aligned} \tag{99}$$

or equally as

$$\begin{aligned}\tilde{\chi}^2{}_{\text{Calculated}}\left(A_{\text{t}} \leftrightarrow B_{\text{t}} \mid B\right) &\equiv \frac{\left(a-(a+c)\right)^2}{B}+ \\ &\quad \frac{d-\left((b+d)\right)^2}{\underline{B}} \\ &\equiv \frac{c^2}{B}+\frac{b^2}{\underline{B}}\end{aligned} \tag{100}$$

The calculated $\tilde{\chi}^2$ goodness of fit test of a necessary and sufficient condition relationship can be compared with a theoretical chi-square value at a certain level of significance α. Under conditions where the observed values are equal to the expected/theoretical values of a necessary and sufficient condition relationship/distribution $\text{p}(\text{A}_{\text{t}} \leftrightarrow \text{B}_{\text{t}})$, the $\tilde{\chi}^2$-distribution equals zero. It is to be cleared whether Yate's (Yates, 1934) continuity correction should be used at all.

2.2.17. The left-tailed p Value of a necessary and sufficient condition relationship

Definition 2.48 (The left-tailed p Value of a necessary and sufficient condition relationship).

The left-tailed (lt) p Value (Barukčić, 2019c) of a necessary and sufficient condition relationship can be calculated as follows.

$$\begin{aligned}pValue_{\text{lt}}\left(A_{\text{t}} \leftrightarrow B_{\text{t}}\right) &\equiv 1-e^{-(1-p(A_{\text{t}} \leftrightarrow B_{\text{t}}))} \\ &\equiv 1-e^{-((b+c)/N)}\end{aligned} \tag{101}$$

In this context, a low p-value indicates again a statistical significance. Table 8 may provide an overview of the theoretical distribution of a necessary and sufficient condition.

Table 8. Necessary and sufficient condition.

		Conditioned B_{t}		
		YES	NO	
Condition A_{t}	YES	1	0	1
	NO	0	1	1
		1	1	2

2.2.18. Either or conditions

Definition 2.49 (Either A_{t} or B_{t} conditions [*NEQV*]).

Mathematically, an either A_t or B_t condition relationship (NEQV), denoted by $p(A_t \succ\!\prec B_t)$ in terms of statistics and probability theory, is defined(Barukčić, 1989, p. 68-70) as

$$\begin{aligned} p\left(A_t \succ\!\prec B_t\right) &\equiv \frac{\sum_{t=1}^{N}\left(\left(A_t \wedge \underline{B}_t\right) \vee \left(\underline{A}_t \wedge B_t\right)\right)}{N} \\ &\equiv p\left(b_t\right) + p\left(c_t\right) \\ &\equiv \frac{N \times \left(p\left(b_t\right) + p\left(c_t\right)\right)}{N} \\ &\equiv \frac{b+c}{N} \\ &\equiv +1 \end{aligned} \tag{102}$$

It is $p\left(A_t \succ\!\prec B_t\right) \equiv 1 - p\left(A_t <\!\!\succ B_t\right)$ (see Table 9).

Table 9. Either A_t or B_t relationship.

		Conditioned B_t		
		YES	NO	
Condition A_t	YES	0	1	1
	NO	1	0	1
		1	1	2

2.2.19. The Chi-square goodness of fit test of an either or condition relationship

Definition 2.50 (The $\tilde{\chi}^2$ goodness of fit test of an either or condition relationship).

An either or condition relationship $p(A_t \succ\!\prec B_t)$ can be tested by the chi-square distribution (also chi-squared or $\tilde{\chi}^2$-distribution) too. The $\tilde{\chi}^2$ goodness of fit test of an either or condition relationship with degree of freedom (d. f.) of d. f. = 1 is calculated as

$$\begin{aligned} \tilde{\chi}^2{}_{\text{Calculated}}\left(\left(A_t \succ\!\prec B_t\right) \mid A\right) &\equiv \frac{\left(b-\left(a+b\right)\right)^2}{A} + \\ &\quad \frac{c-\left(\left(c+d\right)\right)^2}{\underline{A}} \\ &\equiv \frac{a^2}{A} + \frac{d^2}{\underline{A}} \end{aligned} \tag{103}$$

or equally as

$$\begin{aligned}\tilde{\chi}^2{}_{\text{Calculated}}\left((A_{\text{t}} \succ\!\prec B_{\text{t}}) \mid B\right) &\equiv \frac{(c-(a+c))^2}{B}+ \\ &\quad \frac{b-((b+d))^2}{\underline{B}} \\ &\equiv \frac{a^2}{B}+\frac{d^2}{\underline{B}}\end{aligned} \tag{104}$$

Yate's (Yates, 1934) continuity correction has not been used in this context.

2.2.20. The left-tailed p Value of an either or condition relationship

Definition 2.51 (The left-tailed p Value of an either or condition relationship).

The left-tailed (lt) p Value (Barukčić, 2019c) of an either or condition relationship can be calculated as follows.

$$\begin{aligned}pValue_{\text{lt}}\left(A_{\text{t}} \succ\!\prec B_{\text{t}}\right) &\equiv 1-e^{-(1-p(A_{\text{t}}>-<B_{\text{t}}))} \\ &\equiv 1-e^{-((a+d)/N)}\end{aligned} \tag{105}$$

In this context, a low p-value indicates again a statistical significance.

2.2.21. Causal relationship k

The history of the denialism of causality in Philosophy, Mathematics, Statistics, Physics et cetera is very long. We only recall David Hume's (1711-1776) account of causation and his inappropriate reduction of the cause-effect relationship to a simple habitual connection in human thinking or Immanuel Kant's (1724-1804) initiated trial to consider causality as nothing more but a '*a priori*'given category (Langsam, 1994) in human reasoning and other similar attempts too. It is worth noting in this context that especially Karl Pearson (1857 - 1936) himself has been engaged in a long lasting and never-ending crusade against causation too. "**Pearson categorically denies the need for an independent concept of causal relation beyond correlation ... he *exterminated* causation from statistics before it had a chance to take root** "(Pearl, 2000) At the beginning of the 20th century notable proponents of **conditionalism** like the German anatomist and pathologist David Paul von Hansemann (Hansemann, David Paul von, 1912) (1858 - 1920) and the biologist and physiologist Max Richard Constantin Verworn(Verworn, 1912) (1863 - 1921) started a new attack(Kröber, 1961) on the principle of causality. In his essay "Kausale und konditionale Weltanschauung"Verworn(Verworn, 1912) presented "an exposition of 'conditionism'as contrasted with 'causalism,'(Unknown, 1913) while ignoring cause and effect relationships completely. "**Das Ding ist also identisch mit der Gesamtheit seiner Bedingungen**."(Verworn, 1912) However, Verworn's goal to exterminate causality completely out of science was hindered by the further development of research. The history of futile attempts to refute **the principle of causality** culminated in a publication by the German born physicist Werner Karl Heisenberg (1901 - 1976). Heisenberg put forward an illogical, inconsistent and confusing uncertainty principle which opened the door to wishful thinking and logical fallacies in physics and in science as such. Heisenberg's unjustified reasoning ended in an act of a manifestly unfounded conclusion: "**Weil alle Experimente den Gesetzen der Quantenmechanik und damit der Gleichung (1) unterworfen sind, so wird durch die Quantenmechanik die Ungültigkeit des Kausalgesetzes definitiv festgestellt**."(Heisenberg, Werner Karl, 1927) while 'Gleichung (1)'denotes Heisenberg's uncertainty principle. Einstein's himself, a major contributor to quantum theory and in the same respect a major critic of quantum theory, disliked Heisenberg's uncertainty principle fundamentally while Einstein's opponents used Heisenberg's Uncertainty Principle against Einstein. After the End of the German Nazi initiated Second World War with unimaginable brutality and high human losses and a death toll due to an industrially organised mass killing of people by the German Nazis which did not exist in this way before, Werner Heisenberg visited Einstein in Princeton (New Jersey, USA) in October 1954 (Neffe, 2006). Einstein agreed to meet Heisenberg only for a very short period of time but their encounter lasted longer. However, there where not only a number of differences between Einstein and Heisenberg, these two physicists did not really loved each other. "Einstein remarked that the inventor of the uncertainty principle was a 'big Nazi'... "(Neffe, 2006) Albert Einstein (1879 - 1955) took again the opportunity to refuse to endorse **Heisenberg's uncertainty principle** as a fundamental law of nature and rightly too. Meanwhile, Heisenberg's uncertainty principle is refuted (see Barukčić, 2011a, 2014, 2016a) for several times but still not exterminated completely out of physics and out of science as such. In contrast to such extreme anti-causal positions as advocated by Heisenberg and the **Copenhagen interpretation of quantum mechancis**, the search for a (mathematical) solution of *the issue of causal inferences* is as old as human mankind itself ("*i. e. Aristotle's Doctrine of the Four Causes*") (Hennig, 2009) even if there is still little to go on. It is appropriate to specify especially

the position of D'Holbach(Holbach, Paul Henri Thiry Baron de, 1770). D'Holbach (1723-1789) himself linked cause and effect or causality as such to changes. "**Une *cause*, est un être qui e met un autre en mouvement, ou qui produit quelque changement en lui. *L'effet* est le changement qu'un corps produit dans un autre ...**"(Holbach, Paul Henri Thiry Baron de, 1770) D'Holbach infers in the following: "**De l'action et de la réaction continuelle de tous les êtres que la nature renferme, il résulte une suite de causes et d'effets ..**"(Holbach, Paul Henri Thiry Baron de, 1770) With more or less meaningless or none progress on the matter in hand even in the best possible conditions, it is not surprising that authors are suggesting more and more different approaches and models for causal inference. Indeed, the hope is justified that logically consistent *statistical methods of causal inference* can help scientist to achieve so much with so little. One of the methods of causal inference in Bio-sciences are based on the known *Henle(Henle, 1840) (1809–1885) - Koch(Koch, 1878) (1843–1910) postulates* (Carter, 1985) which are applied especially for the identification of a causative agent of an (infectious) disease. However, the pathogenesis of most chronic diseases is more or less very complex and potentially involves the interaction of several factors. In practice, from the 'pure culture' requirement of the Henle-Koch postulates insurmountable difficulties may emerge. In light of subsequent developments (PCR methodology, immune antibodies et cetera) it is appropriate to review the full validity of the Henle-Koch postulates in our days. In 1965, Sir Austin Bradford Hill (Hill, 1965) published nine criteria (the '*Bradford Hill Criteria* ') in order to determine whether observed epidemiologic associations are causal. Somewhat worrying, is at least the fact that, Hill's "... fourth characteristic is *the temporal relationship of the association* " and so-to-speak just a reformulation of the '*post hoc ergo propter hoc'(Barukčić, 1989, Woods and Walton, 1977)* logical fallacy through the back-door and much more then this. It is questionable whether association as such can be treated as being identical with causation. Unfortunately, due to several reasons, it seems therefore rather problematic to rely on Bradford Hill Criteria carelessly. Meanwhile, several other and competing mathematical or statistical approaches for causal inference have been discussed (Barukčić, 1989, 1997, 2005, 2016b, 2017a,c, Bohr, 1937, Dempster, 1990, Espejo, 2007, Hessen, Johannes, 1928, Hesslow, 1976, 1981, Korch, Helmut, 1965, Pearl, 2000, Schlick, Friedrich Albert Moritz, 1931, Suppes, 1970, Zesar, 2013) or even established (Barukčić, 1989, 1997, 2005, 2016b, 2017a,c). Nevertheless, the question is still not answered, is it at all possible to establish a cause effect relationship between two factors while applying only certain statistical (Sober, 2001) methods?

Definition 2.52 (**Causal relationship k**).

Nonetheless, mathematically, the causal(Barukčić, 2011a,b, 2012) relationship (Barukčić, 1989, 1997, 2005, 2016b, 2017a,c, 2021d) between a cause U_t (German: Ursache) and an effect W_t (German: Wirkung), denoted by k(U_t, W_t), is defined *at each single(Thompson, 2006) Bernoulli trial t* in terms of statistics and probability theory as

$$\begin{aligned} k\left(U_t,W_t\right) &\equiv \frac{\sigma\left(U_t,W_t\right)}{\sigma\left(U_t\right)\times\sigma\left(W_t\right)} \\ &\equiv \frac{p\left(U_t\wedge W_t\right)-p\left(U_t\right)\times p\left(W_t\right)}{\sqrt[2]{\left(p\left(U_t\right)\times\left(1-p\left(U_t\right)\right)\right)\times\left(p\left(W_t\right)\times\left(1-p\left(W_t\right)\right)\right)}} \end{aligned} \tag{106}$$

where σ (U_t , W_t) denotes the co-variance between a cause U_t and an effect W_t *at every single*

Bernoulli trial t, σ (U_t) denotes the standard deviation of a cause U_t at the same single Bernoulli trial t, σ (W_t) denotes the standard deviation of an effect W_t at same single Bernoulli trial t. Table 10 illustrates the theoretically possible relationships between a cause and an effect.

Table 10. Sample space and the causal relationship k

		Effect B_t		
		TRUE	FALSE	
Cause	TRUE	$p(a_t)$	$p(b_t)$	$p(U_t)$
A_t	FALSE	$p(c_t)$	$p(d_t)$	$p(\underline{U}_t)$
		$p(W_t)$	$p(\underline{W}_t)$	+1

However, even if one thinks to recognise the trace of Bravais (Bravais, 1846) (1811-1863) - Pearson's (1857-1936) "*product-moment coefficient of correlation*"(Galton, 1877, Pearson, 1896) inside the causal relationship k (Barukčić, 1989, 1997, 2005, 2016b, 2017a,c) both are completely different. According to Pearson: "*The fundamental theorems of correlation were for the first time and almost exhaustively discussed by B r a v a i s ('Analyse mathematique sur les probabilities des erreurs de situation d'un point.' Memoires par divers Savans, T. IX., Paris, 1846, pp. 255-332) nearly half a century ago.*"(Pearson, 1896) Neither does it make much sense to elaborate once again on the issue causation(Blalock, 1972) and correlation, since both are not identical (Sober, 2001) nor does it make sense to insist on the fact that "*Pearson's philosophy discouraged him from looking too far behind phenomena.*"(Haldane, 1957) Whereas it is essential to consider that the causal relationship k, in contrast to Pearson's product-moment coefficient of correlation(Pearson, 1896) or to Pearson's phi coefficient(Pearson, 1904b), is defined at every single Bernoulli trial t. This might be a very *small* difference. However, even a small difference might determine a difference. However, in this context and in any case, this small difference *makes*(Barukčić, 2018a) the difference.

2.2.22. Cause and effect

Definition 2.53 (Cause and effect).

What is the cause, what is the effect? Under conditions of a **positive** causal relationship k, an event U_t which is for sure a cause of another event W_t is at the same time t a necessary and sufficient condition of an event W_t. Table 11 may illustrate this relationship.

As can be seen, there is a kind of strange mirroring between U_t and W_t at the same Bernoulli trial t. Lastly, both are converses of each other too. In other words, U_t's being a necessary condition of W_t's is equivalent to W_t's being a sufficient condition of U_t's (and vice versa). In general, it is

$$(U_t \vee \underline{W}_t) \equiv (\underline{W}_t \vee U_t) \equiv ((U_t \vee \underline{W}_t) \wedge (\underline{W}_t \vee U_t)) \equiv +1 \tag{107}$$

In our everyday words,

Table 11. What is the cause, what is the effect?

		Effect W_t		
		TRUE	FALSE	
Cause	TRUE	**+1**	**+0**	$p(U_t)$
U_t	FALSE	**+0**	**+1**	$p(\underline{U}_t)$
		$p(W_t)$	$p(\underline{W}_t)$	+1

without

U_t

no

W_t

is equivalent with

if

W_t

then

U_t

and vice versa.

Necessary and sufficient conditions are relationships used to describe the relationship between two events at the same Bernoulli trial t. In more detail, if U_t then W_t is equivalent with W_t is necessary for U_t, because the truth of U_t guarantees the truth of W_t. In general, it is

$$(\underline{U}_t \vee W_t) \equiv (W_t \vee \underline{U}_t) \equiv ((\underline{U}_t \vee W_t) \wedge (W_t \vee \underline{U}_t)) \equiv +1 \tag{108}$$

In other words, it is impossible to have U_t without W_t (Bloch, 2011). Similarly, U_t is sufficient for W_t, because U_t being true always implies that W_t is true, but U_t not being true does not always imply that W_t is not true.

For instance, **without** gaseous oxygen (U_t), there would be **no** burning wax candle (W_t); hence the relationship **if** burning wax candle (W_t) **then** gaseous oxygen (U_t) is equally true and given.

This simple example may illustrate the reason why a sufficient condition alone is not enough to describe a cause completely. The relationship **if** burning wax candle (W_t) **then** gaseous oxygen (U_t) is given. Independently of this fact, a burning wax candle is not the cause of gaseous oxygen. Therefore, in order to be a cause of oxygen, additional evidence is necessary that a burning wax candle is a

necessary condition of gaseous oxygen too. However, even if the relationship **without** gaseous oxygen **no** burning wax candle is given, this relationship is not given vice versa. The relationship **without** burning wax candle **no** gaseous oxygen is not given. Like other fundamental concepts, the concepts of cause and effect can be associated with difficulties too. In order to recognise a causal relationship between U_t and W_t, it is necessary that the same study or that at least different studies provide evidence of a necessary condition between U_t and W_t and of a sufficient condition between U_t and W_t and if possible of **a necessary and sufficient condition** between U_t and W_t too.

Mathematically, a necessary and sufficient condition between U_t and W_t is defined as

$$(U_t \vee \underline{W}_t) \wedge (\underline{U}_t \vee W_t) \equiv +1 \tag{109}$$

However, I think it necessary to make a clear distinction between a necessary and sufficient condition and the converse relationship (Eq. 107) above.

$$((U_t \vee \underline{W}_t) \wedge (\underline{W}_t \vee U_t)) \neq (U_t \vee \underline{W}_t) \wedge (\underline{U}_t \vee W_t) \tag{110}$$

2.3. Statistical methods

The probability of the necessary (Barukčić, 2021d) condition p(SINE) has been calculated and tested for statistical significance. The probability of the sufficient (Barukčić, 2021d) condition p(IMP) has been calculated, the statistical significance of this relationship has been proofed. The chi-square goodness of fit test with one degree of freedom has been used to test whether the sample data published fit a certain theoretical distribution in the population. The causal relationship k (Barukčić, 2021d) has been calculated to evaluate a possible causal relationship between the events/factors analysed. The hyper-geometric(Fisher, 1922, Gonin, 1936, Huygens and van Schooten, 1657, Pearson, 1899) distribution (HGD) has been used to test the one-sided significance of the causal relationship k. The study (design) bias has been controlled by IOI, the index of independence(Barukčić, 2019a) and IOU, the index of unfairness(Barukčić, 2019b). All the data were analysed using MS Excel (Microsoft Corporation, USA). The p values less than 0.05 were considered to indicate a statistically significant difference.

2.4. Axioms

2.4.1. Axiom I. Lex identitatis

In this context, we define axiom I as the expression

$$+1 = +1 \tag{111}$$

2.4.2. Axiom II. Lex contradictionis

In this context, axiom II or **lex contradictionis**, the negative of lex identitatis, or

$$+0 = +1 \tag{112}$$

and equally the most simple form of a contradiction formulated.

2.4.3. Axiom III. Lex negationis

$$\neg(0) \times 0 = 1 \tag{113}$$

where $\neg$ denotes (logical (Boole, 1854) or natural) negation (Ayer, 1952, Förster and Melamed, 2012, Hedwig, 1980, Heinemann, Fritz H., 1943, Horn, 1989, Koch, 1999, Kunen, 1987, Newstadt, 2015, Royce, 1917, Speranza and Horn, 2010, Wedin, 1990). In this context, there is some evidence that $\neg(1) \times 1 = 0$. In other words, it is $(\neg(1) \times 1) \times (\neg(0) \times 0) = 1$

3. Results

3.1. Causal relationship and study design

Theorem 3.1 (Causal relationship and study design)**.** *An essential key condition to ensure a comparability of the results of experimental and non-experimental studies which aim to investigate a cause-effect relationship between events is an index of independence of*

$$p\left(IOI\left(A_t,\underline{B}_t\right)\right) \equiv Absolute\left(\frac{A_t+\underline{B}_t}{N}-1\right) \equiv +0 \tag{114}$$

Proof by direct proof. The premise

$$+1 \equiv +1 \tag{115}$$

is true. Multiple definitions of causation have been offered in science. But despite much discussion about causation, it is clear that an effect cannot exist without a cause. In other words, without a cause (A_t), no effect (B_t). A necessary condition relationship between cause and effect is one determining part of a deterministic causal relationship, and appears to best fit the characteristics of a useful definition of causation. In the following, we rearrange the premise (see equation 88, p. 37) and do obtain

$$p\left(A_t \leftarrow B_t\right) \equiv +1 \tag{116}$$

Logically consistent definitions of deterministic causation need to consider, how to characterize a cause. Another aspect of deterministic causation is the need that a cause produces its own effect. In other words, if cause, then effect. In the following, we rearrange equation 116 and do obtain (see equation 93, p. 40)

$$p\left(A_t \leftarrow B_t\right) \equiv p\left(A_t \rightarrow B_t\right) \tag{117}$$

Equation 117 draws attention to the fact that a cause is a necessary and sufficient condition of an effect. Table 12 is providing an overview of this relationship.

Table 12. Necessary and sufficient condition and causal relationship

		Effect B_t		
		TRUE	FALSE	
Cause	TRUE	+1	+0	$p(A_t)$
A_t	FALSE	+0	+1	$p(\underline{A}_t)$
		$p(B_t)$	$p(\underline{B}_t)$	+1

In case of a contra-valent relationship (either A_t or B_t), we expect the relationship,

$$1-p\left(A_t \leftarrow B_t\right) \equiv 1-p\left(A_t \rightarrow B_t\right) \tag{118}$$

which has no influence whatsoever on the progress of this investigation. Nevertheless, equation 117 changes (see equation 88, p. 37). It is

$$\frac{a_t + \underline{B_t}}{N} \equiv p\left(A_t \rightarrow B_t\right) \tag{119}$$

Equation 119 becomes (see equation 93, p. 40)

$$\frac{a_t + \underline{B_t}}{N} \equiv \frac{a_t + \underline{A_t}}{N} \tag{120}$$

Equation 120 simplifies as

$$a_t + \underline{B_t} \equiv a_t + \underline{A_t} \tag{121}$$

or as

$$\underline{B_t} \equiv \underline{A_t} \tag{122}$$

or as

$$N - B_t \equiv N - A_t \tag{123}$$

or as

$$B_t \equiv A_t \tag{124}$$

and as

$$\underline{B_t} \equiv N - A_t \tag{125}$$

Rearranging equation 125 it is

$$A_t + \underline{B_t} \equiv N \tag{126}$$

Equation 126 changes to

$$\frac{A_t + \underline{B_t}}{N} \equiv +1 \tag{127}$$

and to

$$\frac{A_t + \underline{B_t}}{N} - 1 \equiv +0 \tag{128}$$

The study design of a study which aims to investigate a cause-effect relationship (see equation 117) between events should ensure as much as possible an index of independence(Barukčić, 2019a) (IOI) as

$$IOI\left(A_t, \underline{B_t}\right) \equiv \frac{A_t + \underline{B_t}}{N} - 1 \equiv +0 \tag{129}$$

Taking the absolute value from equation 129, we obtain the value of the index of independence(Barukčić, 2019a) (IOI) as

$$p\left(IOI\left(A_t, \underline{B_t}\right)\right) \equiv \text{Absolute}\left(\frac{A_t + \underline{B_t}}{N} - 1\right) \equiv +0 \tag{130}$$

□

This result is valid for a contra-valent relationship (either A_t or B_t) and an exclusion relationship (A_t excludes B_t and vice versa) too.

3.2. Independence of events

In order to characterize the relationship between cause and effect while using the tools of probability theory (i.e. probabilistic [28] causation), it is necessary to address at least one preliminary issue, the relationship between the law of independence and the relationship between cause and effect. The scientific concept of independence (Einstein, 1948, Kolmogoroff, Andreĭ Nikolaevich, 1933, Moivre, 1718) is of fundamental importance in (natural) sciences. Einstein himself puts it in a nutshell: "*Ohne die Annahme einer ··· Unabhängigkeit der ··· Dinge voneinander ··· wäre physikalisches Denken ··· nicht möglich.*"(Einstein, 1948). In general, a minimum requirement for any concept of causation is the possibility of a method to demonstrate the absence of independence at the same (period of) time Bernoulli trial t between events with certainty.

Theorem 3.2 (Independence of events)**.** *In general, assuming independence of the events A_t and B_t, it holds that*

$$\frac{N \times a_t}{A_t} \equiv B_t \tag{131}$$

Proof by direct proof. In the case of independence of events, it is

$$p\left(A_{\mathrm{t}} \wedge B_{\mathrm{t}}\right) \equiv p\left(a_{\mathrm{t}}\right) \equiv p\left(A_{\mathrm{t}}\right) \times p\left(B_{\mathrm{t}}\right) \tag{132}$$

Multiplying equation 132 by the sample size / population's size N^2, while the probability of an event is constant from trial to trial, it is

$$N^2 \times p\left(a_{\mathrm{t}}\right) \equiv N \times p\left(A_{\mathrm{t}}\right) \times N \times p\left(B_{\mathrm{t}}\right) \tag{133}$$

Simplifying equation 133, it is

$$N \times a_{\mathrm{t}} \equiv A_{\mathrm{t}} \times B_{\mathrm{t}} \tag{134}$$

Equation 134 is rearranged as

$$\frac{N \times a_{\mathrm{t}}}{A_{\mathrm{t}}} \equiv B_{\mathrm{t}} \tag{135}$$

□

3.3. Bias and index of independence

Random error or lack of precision and other factors while investigating a relationship between a cause (i.e. an exposure) and an effect cannot be excluded completely or absolutely and can cause false

[28] Parascandola M. Causes, risks, and probabilities: probabilistic concepts of causation in chronic disease epidemiology. Prev Med. 2011 Oct;53(4-5):232-4. doi: 10.1016/j.ypmed.2011.09.007. Epub 2011 Oct 5. PMID: 21983603.

conclusions and be potentially misleading. In general, bias [29] , [30] , [31] , [32] in research as determined by the deviation of data collection, data analysis, data interpretation, publication et cetera from the truth can occur either unintentionally or intentionally. It is necessary to undertake all known actions available to reduce or minimize bias as much as possible. In spite of that, or exactly because of that, the question arises whether bias can be induced by an index of independence. A study design which is based on an index of independence need to ensure to recognize an independence of events without any restriction.

Theorem 3.3 (Bias and index of independence)**.** *A study design which is based on the index of independence enables the detection of independent events. In this case, it is for example*

$$p\left(A_t\right)^2 \equiv p\left(a_t\right) \tag{136}$$

Proof by direct proof. The premise

$$+1 \equiv +1 \tag{137}$$

is true. In the following, we rearrange the premise. We obtain

$$A_{\mathrm{t}} \equiv A_{\mathrm{t}} \tag{138}$$

The index of independence is based on the relationship $A_{\mathrm{t}} \equiv B_{\mathrm{t}}$ (see equation 124). Equation 138 becomes

$$A_{\mathrm{t}} \equiv B_{\mathrm{t}} \tag{139}$$

Equation 139 changes to (see equation 135)

$$A_{\mathrm{t}} \equiv \frac{N \times a_{\mathrm{t}}}{A_{\mathrm{t}}} \tag{140}$$

Simplifying equation 140, we obtain

$$A_{\mathrm{t}} \times A_{\mathrm{t}} \equiv N \times a_{\mathrm{t}} \tag{141}$$

Dividing equation 141 by N^2, it is

$$\frac{A_{\mathrm{t}} \times A_{\mathrm{t}}}{N \times N} \equiv \frac{N \times a_{\mathrm{t}}}{N \times N} \tag{142}$$

or

$$p\left(A_{\mathrm{t}}\right)^2 \equiv p\left(a_{\mathrm{t}}\right) \tag{143}$$

□

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Theorem 3.4 (Relative risk and causal relationship k)**.** *Under certain specific circumstances, the relative risk demands that the causal relationship k is given by the equation*

$$k\left(A_t,B_t\right)\equiv\frac{\left(p\left(A_t\right)\times RR\left(A_t,B_t\right)_{nc}\times\frac{p\left(c_t\right)}{p\left(NotA_t\right)}\right)-p\left(A_t\right)\times p\left(B_t\right)}{\sqrt[2]{\left(p\left(A_t\right)\times\left(1-p\left(A_t\right)\right)\right)\times\left(p\left(B_t\right)\times\left(1-p\left(B_t\right)\right)\right)}}\tag{144}$$

Proof by direct proof. The premise

$$+1\equiv+1\tag{145}$$

is true. In the following, we rearrange the premise. The relative (Cornfield, 1951, Sadowsky et al., 1953) risk (see Barukčić, 2021c) is denoted as $RR(A_t,B_t)_{nc}$. We obtain

$$RR\left(A_t,B_t\right)_{nc}\equiv RR\left(A_t,B_t\right)_{nc}\tag{146}$$

Equation 146 changes according to equation 55 to

$$\frac{\frac{p(a_t)}{p(A_t)}}{\frac{p(c_t)}{p(NotA_t)}}\equiv RR\left(A_t,B_t\right)_{nc}\tag{147}$$

and to

$$p\left(a_t\right)\equiv p\left(A_t\right)\times RR\left(A_t,B_t\right)_{nc}\times\frac{p\left(c_t\right)}{p\left(NotA_t\right)}\tag{148}$$

The causal relationship itself is defined (see equation 106) as

$$k\left(A_t,B_t\right)\equiv\frac{p\left(a_t\right)-p\left(A_t\right)\times p\left(B_t\right)}{\sqrt[2]{\left(p\left(A_t\right)\times\left(1-p\left(A_t\right)\right)\right)\times\left(p\left(B_t\right)\times\left(1-p\left(B_t\right)\right)\right)}}\tag{149}$$

We substitute the result of equation 148 into equation 149. There are circumstances where the relationship between the relative risk and the causal relationship k is given by the relationship

$$k\left(A_t,B_t\right)\equiv\frac{\left(p\left(A_t\right)\times RR\left(A_t,B_t\right)_{nc}\times\frac{p\left(c_t\right)}{p\left(NotA_t\right)}\right)-p\left(A_t\right)\times p\left(B_t\right)}{\sqrt[2]{\left(p\left(A_t\right)\times\left(1-p\left(A_t\right)\right)\right)\times\left(p\left(B_t\right)\times\left(1-p\left(B_t\right)\right)\right)}}\tag{150}$$

□

Theorem 3.5 (Odds ratio and causal relationship k)**.** *Under specific circumstances, an odds ratio determines the causal relationship k by the equation*

$$k\left(A_t,B_t\right)\equiv\frac{\left(p\left(b_t\right)\times OR\left(A_t,B_t\right)\times\left(\frac{p\left(c_t\right)}{p\left(d_t\right)}\right)\right)-p\left(A_t\right)\times p\left(B_t\right)}{\sqrt[2]{\left(p\left(A_t\right)\times\left(1-p\left(A_t\right)\right)\right)\times\left(p\left(B_t\right)\times\left(1-p\left(B_t\right)\right)\right)}}\tag{151}$$

Proof by direct proof. The premise

$$+1 \equiv +1 \tag{152}$$

is true. In the following, we rearrange the premise. An odds ratio (Cox, 1958, Fisher, 1935, p. 50) as the ratio of the odds of an event occurring in one group with respect to the odds of its occurring in another group is denoted as $OR(A_t, B_t)$. We obtain

$$OR(A_t, B_t) \equiv OR(A_t, B_t) \tag{153}$$

Equation 153 becomes

$$\left(\frac{(a_t) \times (d_t)}{(b_t) \times (c_t)}\right) \equiv \left(\frac{N \times p(a_t) \times N \times p(d_t)}{N \times p(b_t) \times N \times p(c_t)}\right) \equiv \left(\frac{p(a_t)}{p(b_t)}\right) / \left(\frac{p(c_t)}{p(d_t)}\right) \equiv OR(A_t, B_t) \tag{154}$$

Equation 154 becomes

$$p(a_t) \equiv p(b_t) \times OR(A_t, B_t) \times \left(\frac{p(c_t)}{p(d_t)}\right) \tag{155}$$

The causal relationship itself is defined (see equation 106) as

$$k(A_t, B_t) \equiv \frac{p(a_t) - p(A_t) \times p(B_t)}{\sqrt[2]{(p(A_t) \times (1 - p(A_t))) \times (p(B_t) \times (1 - p(B_t)))}} \tag{156}$$

We substitute the result of equation 155 into equation 156. Under specific circumstances, an odds ratio defines the causal relationship k by the equation

$$k(A_t, B_t) \equiv \frac{\left(p(b_t) \times OR(A_t, B_t) \times \left(\frac{p(c_t)}{p(d_t)}\right)\right) - p(A_t) \times p(B_t)}{\sqrt[2]{(p(A_t) \times (1 - p(A_t))) \times (p(B_t) \times (1 - p(B_t)))}} \tag{157}$$

□

4. Discussion

Any study design [33] with its very own strengths and weaknesses has the potential of clouding our view of the essential and to endanger among other the possibility to arrive at correct study conclusions. Therefore, several aspects of a study design [34] , [35] , [36] , [37] need to be addressed very carefully in the design phase of any study, otherwise problems and contradictions (see Hegel, Georg Wilhelm Friedrich, 1812, 1813, 1816) are pre-ordained. The selection of a study design need to incorporate consideration of several aspects, including sample size calculations, too. An appropriate selection of a study design is only one of the many elements in successful research. Sample size calculations are not of minor importance too. In general, a sample that is too large might induce a waste of time, money and harm people, while a sample size which is too small [38] might not be able to detect any effect. The design [39] of studies that seek to investigate cause-and-effect [40] , [41] relationships between events needs to be a lot more careful and should pay special attention to the requirement of an index of independence as much as possible near to zero or

$$p\left(IOI\left(A_{\mathrm{t}},\underline{B}_{\mathrm{t}}\right)\right)\equiv \text{Absolute}\left(\frac{A_{\mathrm{t}}+\underline{\underline{B_{\mathrm{t}}}}}{N}-1\right)\equiv +0 \tag{158}$$

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5. Conclusion

An index of independence very close to zero is of strong advantage in order to detect causal relationship in experimental and non-experimental (medical) research.

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Private note

The definition section of a paper need not and does not necessarily contain new scientific aspects. Above all, it also serves to better understand a scientific publication, to follow every step of the arguments of an author and to explain in greater details the fundamentals on which a publication is based. Therefore, there is no objective need to force authors to reinvent a scientific wheel once and again unless such a need appears obviously factually necessary. The effort to write about a certain subject in an original way in multiple publications does not exclude the necessity simply to cut and paste from an earlier work, and has nothing to do with self-plagiarism. However, such an attitude cannot simply be transferred to the sections' introduction, results, discussion and conclusions et cetera.

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