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Human papillomavirus is the cause of human invasive cervical cancer

Research article

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Abstract

Background:

The study of Lei et al. has been re-analysed.

Methods:

New statistical methods were used.

Results:

The study of Lei et al. with a sample size of N = 1672983 confirmed Barukčić's 2018 hypothesis.

Conclusion:

Human papillomavirus is the cause of human cervical cancer.

Keywords: Cause; Effect; Causal relationship k; Causality; Causation

1. Introduction

A quadrivalent human papillomavirus (HPV) vaccine (HPV types 6, 11, 16, and 18) has the potential to protect against HPV infection, genital warts, and high-grade precancerous cervical lesions et cetera. Jiayao Lei et al. [1] used the nationwide Swedish Total Population Register [2], the Swedish HPV Vaccination Register, the Prescribed Drug Register [3], and the National Vaccination Register to investigate the effectiveness of a quadrivalent human papillomavirus (HPV types 6, 11, 16, and 18) vaccine in preventing high-grade cervical lesions of girls and women who were 10 to 30 years of age. The data as provided by Lei et al. have been re-analysed.

[1]Lei J, Ploner A, Elfström KM, Wang J, Roth A, Fang F, Sundström K, Dillner J, Sparén P. HPV Vaccination and the Risk of Invasive Cervical Cancer. N Engl J Med. 2020 Oct 1;383(14):1340-1348. doi: 10.1056/NEJMoa1917338. PMID: 32997908.

[2]Ludvigsson JF, Almqvist C, Bonamy AK, Ljung R, Michaëlsson K, Neovius M, Stephansson O, Ye W. Registers of the Swedish total population and their use in medical research. Eur J Epidemiol. 2016 Feb;31(2):125-36. doi: 10.1007/s10654-016-0117-y. Epub 2016 Jan 14. PMID: 26769609.

[3]Wettermark B, Hammar N, Fored CM, Leimanis A, Otterblad Olausson P, Bergman U, Persson I, Sundström A, Westerholm B, Rosén M. The new Swedish Prescribed Drug Register–opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiol Drug Saf. 2007 Jul;16(7):726-35. doi: 10.1002/pds.1294. Erratum in: Pharmacoepidemiol Drug Saf. 2008 May;17(5):533. MichaelFored, C [corrected to Fored, Carl Michael]. PMID: 16897791.

2. Material and methods

Scientific knowledge and objective reality are more than only interrelated. It cannot be repeated often enough that objective reality or processes of objective reality is the foundation of any scientific knowledge. Our human experience teaches us however that seen by light, grey is never merely simply grey, and looked at from different angles, many paths may lead to climb up a certain mountain. In general, it is appropriate to ensure as much as possible a broader consideration of a research question and to take into account the different facets and viewpoints of an issue investigated in order to reach a goal.

2.1. Material

2.2. HPV vaccination and cervical cancer I

Lei et al. [4] investigated a study population of at least 1,672,983 girls and women 10 to 30 years of age. In fact, 527,871 of 1,672,983 girls and women received at least one dose of HPV vaccine. According to Lei et al., during the study period, cervical cancer was diagnosed in 538 women who had not received the quadrivalent HPV vaccine and in 19 women who had received the HPV vaccine. The data and the statistical analysis is presented by table 1.

Table 1. HPV vaccine and cervical cancer (Study of Lei et al., 2020).

		Cervical cancer		
		YES	NO	
HPV vaccine	YES	19	527852	527871
	NO	538	1144574	1145112
		557	1672426	1672983

Statistical analysis.	
Causal relationship k =	-0,0110511076
p Value left tailed (HGD) =	0,0000000
p (EXCL) =	0,9999886430
p (EXCL) approx.=	0,9658886894
$\tilde{\chi}^2$ (EXCL— A_t) =	0,0007
$\tilde{\chi}^2$ (EXCL— B_t) =	0,6481
p Value (EXCL) =	0,0000113569
Relative risk (RR).	
RR (nc) =	0,0766
RR (sc) =	0,1081
Additional measures.	
OR =	0,6842
IOR =	-0,8919
Study design.	
p(IOU)=	0,684140245
p(IOI)=	0,315193878

[4] Lei J, Ploner A, Elfström KM, Wang J, Roth A, Fang F, Sundström K, Dillner J, Sparén P. HPV Vaccination and the Risk of Invasive Cervical Cancer. N Engl J Med. 2020 Oct 1;383(14):1340-1348. doi: 10.1056/NEJMoa1917338. PMID: 32997908.

2.3. HPV vaccination and cervical cancer II

However, Lei et al. [5] found that among all vaccinated girls and women about 438,939 (83.2%) initiated vaccination before the age of 17 years. During the study period, cervical cancer was diagnosed only in 2 girls who had received the quadrivalent HPV vaccine before the age of 17 years and in 555 women who had not received the vaccine before the age of 17 years. The data and the statistical analysis is presented by table 2.

Table 2. HPV vaccine before age 17 Yr and cervical cancer (Study Lei et al., 2020).

		Cervical cancer		
		YES	NO	
HPV vaccine before age 17 Yr	YES	2	438937	438939
	NO	555	1233489	1234044
		557	1672426	1672983

Statistical analysis.	
Causal relationship k =	-0,0107351051
p Value left tailed (HGD) =	0,0000000
p (EXCL) =	0,9999988045
p (EXCL) approx.=	0,9964093357
$\tilde{\chi}^2$ (EXCL— A_t) =	0,0000
$\tilde{\chi}^2$ (EXCL— B_t) =	0,0072
p Value (EXCL) =	0,0000011955
Relative risk (RR).	
RR (nc) =	0,0101
RR (sc) =	0,0137
Additional measures.	
OR =	0,7373
IOR =	-0,9863
Study design.	
p(IOU)=	0,737297988
p(IOI)=	0,262036135

2.3.1. 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

[5] Lei J, Ploner A, Elfström KM, Wang J, Roth A, Fang F, Sundström K, Dillner J, Sparén P. HPV Vaccination and the Risk of Invasive Cervical Cancer. N Engl J Med. 2020 Oct 1;383(14):1340-1348. doi: 10.1056/NEJMoa1917338. PMID: 32997908.

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 recognise 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.

2.3.1.1. Index of unfairness (IOU)

Definition 2.1 (Index of unfairness).

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

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

Under ideal conditions, it is desirable that an appropriate study design is able to assure as much as possible an index of unfairness (see Barukčić, 2019c) of 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. Especially under conditions where **a necessary condition relationship or a sufficient condition relationship** is tested, an index of unfairness is of use to prove whether sample data obtained are biased and to what extent.

Table 3. The quality of data (see Barukčić, 2019c, p. 25)

p(IOU)	Quality of study design
$0 < p(IOU) \leq 0,25$	Unfair study design
$0,25 < p(IOU) \leq 0,5$	Very unfair study design
$0,5 < p(IOU) \leq 0,75$	Highly unfair study design
$0,75 < p(IOU) \leq 1,0$	Extremely unfair study design

2.3.1.2. Index of independence (IOI)

Definition 2.2 (Index of independence).

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

$$p\left(IOI\left(A,\underline{B}\right)\right) \equiv Absolute\left(\left(\frac{A+\underline{B}}{N}\right)-1\right) \tag{2}$$

The index of independence(see Barukčić, 2019b) has the potential to indicate the extent to which the study design of a study could be biased.

Table 4. The quality of data (see Barukčić, 2019c, p. 25)

p(IOI)	Quality of study design
$0 < p(IOI) \leq 0,25$	Unfair study design
$0,25 < p(IOI) \leq 0,5$	Very unfair study design
$0,5 < p(IOI) \leq 0,75$	Highly unfair study design
$0,75 < p(IOI) \leq 1,0$	Extremely unfair study design

Under ideal conditions, a 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 appears to be necessary.

2.3.2. Statistical methods

The probability of the exclusion (Barukčić, 2021c) relationship(see also Barukčić, 2021a) p(EXCL) has been calculated and tested for statistical significance. 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. Additionally, the P Value has been calculated approximately (see also Barukčić, 2019d). The causal relationship k (Barukčić, 2016b, 2020a, 2021c) has been calculated to evaluate a possible causal relationship between the events. 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. Bringing different studies together for analysing them or doing a meta-analysis is not without problems. Due to several reasons, there is variability in the data of the studies and there will be differences found. Usually, the heterogeneity among the studies is assessed through I^2 statistics [6] , [7] , [8] . Under usual circumstances, an I^2 value of 25%, 50% and 75% are regarded as low, moderate and high heterogeneity[9]. In this publication, the study (design) bias and the heterogeneity among the studies has been controlled by IOI, the index of independence (Barukčić, 2019b) and IOU, the index of unfairness (Barukčić, 2019c). All the data were analysed using MS Excel (Microsoft Corporation, USA).

[6]Cochran WG. The combination of estimates from different experiments. Biometrics 1954; 10(1): 101-29.

[7]Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002 Jun 15;21(11):1539-58. doi: 10.1002/sim.1186. PMID: 12111919.

[8]Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003 Sep 6;327(7414):557-60. doi: 10.1136/bmj.327.7414.557. PMID: 12958120; PMCID: PMC192859.

[9]Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003 Sep 6;327(7414):557-60. doi: 10.1136/bmj.327.7414.557. PMID: 12958120; PMCID: PMC192859.

P values less than 0.05 were considered statistically significant.

2.4. Methods

Definitions should help us to provide and assure a systematic approach to a scientific issue. It also goes without the need of further saying that a definition as such need to be logically consistent and correct.

2.4.1. 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.

2.4.1.1. The Expectation of a Random Variable

Definition 2.3 (**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 relationship between 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), and the probability p(X), is given by the equation:*

$$\begin{aligned} E(X) &\equiv X \times p(X) \\ &\equiv \Psi(X) \times X \times \Psi^{*}(X) \end{aligned} \tag{3}$$

where $\Psi(X)$ is the wave-function (see Born, 1926, Schrödinger, Erwin Rudolf Josef Alexander, 1926) of X, $\Psi^{*}(X)$ is the complex conjugate wave-function of X. Under conditions where $p(X) \equiv +1$ equation 3 (see p. 76) becomes

$$E(X) \equiv X \tag{4}$$

but not general. The first moment expectation value squared of a random variable X follows as

$$\begin{aligned} E(X)^{2} &\equiv p(X) \times X \times p(X) \times X \\ &\equiv p(X) \times p(X) \times X \times X \\ &\equiv (p(X) \times X)^{2} \\ &\equiv E(X) \times E(X) \end{aligned} \tag{5}$$

The ongoing progress with artificial intelligence has the potential to transform human society far beyond any imaginable border of human recognition and can help even to solve problems that otherwise

would not be tractable. No wonder, scientist and systems are confronted with large volumes of data (big data) of various natures and from different sources. The use of tensor technology can simplify and accelerate Big data analysis. In other words, let $X_{kl\mu\nu\dots}$ denote an n-th index co-variant tensor with the probability $p(X_{kl\mu\nu\dots})$. The first moment expectation value (see Huygens and van Schooten, 1657, Kolmogorov, Andreĭ Nikolaevich, 1950, LaPlace, 1812, Whitworth, 1901) of $X_{kl\mu\nu\dots}$, denoted by $E(X_{kl\mu\nu\dots})$, is a number defined as follows:

$$E\left(X_{kl\mu\nu\dots}\right) \equiv p\left(X_{kl\mu\nu\dots}\right) \times X_{kl\mu\nu\dots} \equiv p\left(X_{kl\mu\nu\dots}\right) \cap X_{kl\mu\nu\dots} \tag{6}$$

while $\times$ or $\cap$ might denote the commutative multiplications of tensors. The first moment expectation value squared of a random variable X follows as

$$\begin{aligned} {}^2E\left(X_{kl\mu\nu\dots}\right) &\equiv p\left(X_{kl\mu\nu\dots}\right) \times X_{kl\mu\nu\dots} \times p\left(X_{kl\mu\nu\dots}\right) \times X_{kl\mu\nu\dots} \\ &\equiv p\left(X_{kl\mu\nu\dots}\right) \times p\left(X_{kl\mu\nu\dots}\right) \times X_{kl\mu\nu\dots} \times X_{kl\mu\nu\dots} \\ &\equiv {}^2\left(p\left(X_{kl\mu\nu\dots}\right) \times X_{kl\mu\nu\dots}\right) \\ &\equiv E\left(X_{kl\mu\nu\dots}\right) \times E\left(X_{kl\mu\nu\dots}\right) \end{aligned} \tag{7}$$

Definition 2.4 (**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:*

$$\begin{aligned} E\left(X^2\right) &\equiv p\left(X\right) \times X^2 \\ &\equiv \left(p\left(X\right) \times X\right) \times X \\ &\equiv E\left(X\right) \times X \\ &\equiv X \times E\left(X\right) \end{aligned} \tag{8}$$

From the point of view of tensor algebra it is

$$\begin{aligned} E\left({}^2X_{kl\mu\nu\dots}\right) &\equiv p\left(X_{kl\mu\nu\dots}\right) \times {}^2X_{kl\mu\nu\dots} \\ &\equiv \left(p\left(X_{kl\mu\nu\dots}\right) \times X_{kl\mu\nu\dots}\right) \times X_{kl\mu\nu\dots} \\ &\equiv E\left(X_{kl\mu\nu\dots}\right) \times X_{kl\mu\nu\dots} \\ &\equiv X_{kl\mu\nu\dots} \times E\left(X_{kl\mu\nu\dots}\right) \end{aligned} \tag{9}$$

Definition 2.5 (**The n-th Moment Expectation of a Random Variable**). *The n-th (see Barukčić, 2020a, 2021c) moment expectation value of a (large) number of independent realizations of a random variable X follows as:*

$$\begin{aligned} E\left(X^n\right) &\equiv p\left(X\right) \times X^n \\ &\equiv \left(p\left(X\right) \times X\right) \times X^{n\text{-}1} \\ &\equiv E\left(X\right) \times X^{n\text{-}1} \end{aligned} \tag{10}$$

2.4.1.2. Probability of a Random Variable What is the nature of the probability of an event, or what is the relationship between probability and geometry or between the probability of an event and notions like false or true. At a first pass, various authors answer this question, one way or another. For authors like De Morgan, probability is only a degree of confidence, or credences or of belief. "By degree of probability, we really mean, or ought to mean, degree of belief" (see De Morgan, 1847, p. 172). Such a purely subjective (or personalist or Bayesian (see Bayes, 1763)) interpretation of probabilities as degrees of confidence, or credences finds its own scientific opposition, moreover, in Kolmogorov's axiomatization of probability theory. However, perhaps we can do better, then, to think that Kolmogorov's axiomatization of probability theory is the last word spoken on probability theory. Nobody seriously considers that Kolmogorov's conceptual apparatus of probability theory has solved the basic problem of any probability theory, the relationship between classical logic or geometry and probability theory. One very massive disadvantage of Kolmogorov's axiomatization of probability theory is that it is very silent especially on this issue. Any unification of geometry and probability theory into one unique mathematical framework might prove very difficult as long as we rely purely on Kolmogorov's understanding of probability theory. It's not surprising that the probability of an event bear at least directly, and sometimes indirectly, upon central philosophical and scientific concerns. A correct understanding of probability is one of the most important foundational scientific problems. Now let us strengthen our position with respect to the probability of an event. In our understanding, the probability of an event is something objectively and real. The probability of an event is the truth value of something or the degree to which something, i.e. a random variable X, is determined by its own expectation value. The probability p(X) of a random variable X follows as (see equation 3)

$$\begin{aligned} p(X) &\equiv \frac{X \times p(X)}{X} \equiv \frac{E(X)}{X} \equiv p(X) \\ &\equiv \frac{X \times X \times p(X)}{X \times X} \equiv \frac{X \times E(X)}{X \times X} \equiv \frac{E\left(X^2\right)}{X^2} \\ &\equiv \frac{E(X)}{X} \equiv \frac{E(X) \times E(X)}{X \times E(X)} \equiv \frac{E(X)^2}{E\left(X^2\right)} \\ &\equiv \frac{E(X)}{X} \equiv \frac{E(X) \times E(\underline{X})}{X \times E(\underline{X})} \equiv \frac{\sigma(X)^2}{X \times X \times (1 - p(X))} \equiv \frac{\sigma(X)^2}{E\left(\underline{X}^2\right)} \\ &\equiv \Psi(X) \times \Psi^*(X) \end{aligned} \tag{11}$$

where $\Psi(X)$ is the wave-function of X, $\Psi^*(X)$ is the complex conjugate wave-function of X. As soon as the probability p(X) of an event X is determined, the probability of its own other, 1 - p(X), the

complementary of X, the opposite of X, anti X, is determined too. We obtain

$$\begin{aligned}
1-p(X) &\equiv 1-\frac{X\times p(X)}{X}\equiv 1-\frac{E(X)}{X}\equiv \frac{X}{X}-\frac{E(X)}{X}\equiv \frac{X-E(X)}{X}\equiv \frac{E(\underline{X})}{X}\equiv p(\underline{X})\\
&\equiv 1-\frac{X\times X\times p(X)}{X\times X}\equiv 1-\frac{X\times E(X)}{X\times X}\equiv 1-\frac{E\left(X^2\right)}{X^2}\equiv \frac{X^2}{X^2}-\frac{E\left(X^2\right)}{X^2}\equiv \frac{X^2-E\left(X^2\right)}{X^2}\\
&\equiv 1-\frac{E(X)}{X}\equiv 1-\frac{E(X)\times E(X)}{X\times E(X)}\equiv 1-\frac{E(X)^2}{E\left(X^2\right)}\\
&\equiv 1-\frac{E(X)}{X}\equiv 1-\frac{E(X)\times E(\underline{X})}{X\times E(\underline{X})}\equiv 1-\frac{\sigma(X)^2}{X\times X\times (1-p(X))}\equiv 1-\frac{\sigma(X)^2}{E\left(\underline{X}^2\right)}\\
&\equiv 1-\Psi(X)\times\Psi^*(X)
\end{aligned} \tag{12}$$

From the point of view of tensor algebra, we obtain

$$\begin{aligned}
p\left(X_{kl\mu\nu\ldots}\right) &\equiv \frac{X_{kl\mu\nu\ldots}\times p\left(X_{kl\mu\nu\ldots}\right)}{X_{kl\mu\nu\ldots}}\equiv \frac{E\left(X_{kl\mu\nu\ldots}\right)}{X_{kl\mu\nu\ldots}}\\
&\equiv \frac{X_{kl\mu\nu\ldots}\times X_{kl\mu\nu\ldots}\times p\left(X_{kl\mu\nu\ldots}\right)}{X_{kl\mu\nu\ldots}\times X_{kl\mu\nu\ldots}}\equiv \frac{E\left({}^2X_{kl\mu\nu\ldots}\right)}{{}^2X_{kl\mu\nu\ldots}}\\
&\equiv \frac{E\left(X_{kl\mu\nu\ldots}\right)\times E\left(X_{kl\mu\nu\ldots}\right)}{E\left(X_{kl\mu\nu\ldots}\right)\times X_{kl\mu\nu\ldots}}\equiv \frac{{}^2E\left(X_{kl\mu\nu\ldots}\right)}{E\left({}^2X_{kl\mu\nu\ldots}\right)}\\
&\equiv \Psi\left(X_{kl\mu\nu\ldots}\right)\times\Psi^*\left(X_{kl\mu\nu\ldots}\right)
\end{aligned} \tag{13}$$

where $\Psi\left(X_{kl\mu\nu\ldots}\right)$ is the wave-function tensor of $X_{kl\mu\nu\ldots}$, $\Psi^*\left(X_{kl\mu\nu\ldots}\right)$ is the complex conjugate wave-function tensor of $X_{kl\mu\nu\ldots}$.

2.4.1.3. Variance of a Random Variable

Definition 2.6 (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, Andreĭ 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 8):

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

while $E(\underline{X}) \equiv X - E(X)$. From the point of view of tensor algebra, it is

$$\begin{aligned}{}^2\sigma\left(X_{kl\mu\nu\ldots}\right) &\equiv E\left({}^2X_{kl\mu\nu\ldots}\right) - {}^2E\left(X_{kl\mu\nu\ldots}\right) \\ &\equiv \left(X_{kl\mu\nu\ldots} \times E\left(X_{kl\mu\nu\ldots}\right)\right) - {}^2E\left(X_{kl\mu\nu\ldots}\right) \\ &\equiv E\left(X_{kl\mu\nu\ldots}\right) \times \left(X_{kl\mu\nu\ldots} - E\left(X_{kl\mu\nu\ldots}\right)\right) \\ &\equiv E\left(X_{kl\mu\nu\ldots}\right) \times E\left(\underline{X}_{kl\mu\nu\ldots}\right)\end{aligned} \tag{15}$$

while $E\left(\underline{X}_{kl\mu\nu\ldots}\right) \equiv X_{kl\mu\nu\ldots} - E\left(X_{kl\mu\nu\ldots}\right)$. As demonstrated by equation 15, variance depends not just on the expectation value of what has actually been observed $E\left(\left(X_{kl\mu\nu\ldots}\right)\right)$, but also on the expectation value that could have been observed but were not $\left(E\left(\underline{X}_{kl\mu\nu\ldots}\right)\right)$. There are circumstances in quantum mechanics where this fact is called the local hidden variable. Even if his might strike us as

peculiar, variance [10] is primarily a mathematical method which is of use in order to evaluate specific hypotheses in the light of some empirical facts. However, as a mathematical tool or method, variance is also a scientific description of a certain part of objective reality too. In this context, as a general mathematical principle, one fundamental meaning of variance is to provide a logically consistent link between something and its own other, between X and anti X.

> "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, 1812a, 1813, 1816) . Based on equation 14, it is

$$E\left(X^2\right) \equiv E(X)^2 + \sigma(X)^2 \tag{16}$$

or

$$\frac{E(X)^2}{E(X^2)} + \frac{\sigma(X)^2}{E(X^2)} \equiv p(X) + \frac{\sigma(X)^2}{E(X^2)} \equiv +1 \tag{17}$$

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

$$\begin{aligned}
\Psi(X) &\equiv \frac{1}{\Psi^*(X)} - \frac{\sigma(X)^2}{(\Psi^*(X) \times E(X^2))} \\
&\equiv \frac{\left(E\left(X^2\right) - \sigma(X)^2\right)}{(\Psi^*(X) \times E(X^2))} \\
&\equiv \frac{1}{(\Psi^*(X) \times E(X^2))} \times \left(E\left(X^2\right) - \sigma(X)^2\right) \\
&\equiv \frac{1}{(\Psi^*(X) \times E(X^2))} \times E(X)^2 \\
&\equiv \frac{1}{\Psi^*(X)} \times \frac{E(X)^2}{E(X^2)} \\
&\equiv \frac{1}{\Psi^*(X) \times X} \times E(X)
\end{aligned} \tag{18}$$

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).

[10] Romeijn, Jan-Willem, "Philosophy of Statistics", The Stanford Encyclopedia of Philosophy (Spring 2022 Edition), Edward N. Zalta (ed.), forthcoming URL = https://plato.stanford.edu/archives/spr2022/entries/statistics/.

Definition 2.7 (**The First Moment Expectation of a Random Variable of $\underline{X}$ (anti X)**). *In general, let $E(\underline{X})$ be defined as*

$$E(\underline{X}) \equiv X - E(X) \equiv X - (X \times p(X)) \equiv X \times (+1 - p(X)) \tag{19}$$

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

$$p(\underline{X}) \equiv 1 - p(X) \tag{20}$$

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:

$$E(\underline{X}) \equiv X - (X \times p(X)) \equiv X \times (1 - p(X)) \equiv X \times p(\underline{X}) \tag{21}$$

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

$$\begin{aligned} E(\underline{X})^2 &\equiv p(\underline{X}) \times X \times p(\underline{X}) \times X \\ &\equiv p(\underline{X}) \times p(\underline{X}) \times X \times X \\ &\equiv (p(\underline{X}) \times X)^2 \\ &\equiv E(\underline{X}) \times E(\underline{X}) \end{aligned} \tag{22}$$

Definition 2.8 (**The Second Moment Expectation of a Random Variable of $\underline{X}$ (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:*

$$\begin{aligned} E(\underline{X}^2) &\equiv p(\underline{X}) \times X^2 \\ &\equiv (p(\underline{X}) \times X) \times X \\ &\equiv E(\underline{X}) \times X \\ &\equiv X \times E(\underline{X}) \end{aligned} \tag{23}$$

Definition 2.9 (**The n-th Moment Expectation of a Random Variable of $\underline{X}$ (anti X)**). *The n-th (see Barukčić, 2020a, 2021c) moment expectation value of a (large) number of independent realizations of a random variable anti X follows as:*

$$\begin{aligned} E(\underline{X}^n) &\equiv p(\underline{X}) \times X^n \\ &\equiv (p(\underline{X}) \times X) \times X^{n\text{-}1} \\ &\equiv E(\underline{X}) \times X^{n\text{-}1} \end{aligned} \tag{24}$$

Definition 2.10 (**The Co-Variance of a Random Variable**). *Sir Ronald Aylmer Fisher (1890 -1962) introduced the term covariance (see Bailey, 1931) in the year 1930 in his book as follows:*

"It is obvious to that where a considerable fraction of the variance is contributed by chance causes, the variance of any group of individuals will be inflated in comparison with the covariances between related groups ... "

(see Fisher, Ronald Aylmer, 1930, p. 195)

In general, the co-variance is defined as given by equation 25.

$$\sigma(X,Y) \equiv E(X,Y) - (E(X) \times E(Y)) \tag{25}$$

From the point of view of tensor algebra, it is

$$\sigma\left(X_{kl\mu\nu\ldots}, Y_{kl\mu\nu\ldots}\right) \equiv E\left(X_{kl\mu\nu\ldots}, Y_{kl\mu\nu\ldots}\right) - \left(E\left(X_{kl\mu\nu\ldots}\right) \times E\left(Y_{kl\mu\nu\ldots}\right)\right) \tag{26}$$

2.4.2. 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 2.11 (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

$$p(A_t) \equiv p(a_t) + p(b_t) \tag{27}$$

The expectation value $E(A_t)$ follows as

$$\begin{aligned} E(A_t) &\equiv A_t \times p(A_t) \\ &\equiv A_t \times (p(a_t) + p(b_t)) \\ &\equiv (A_t \times p(a_t)) + (A_t \times p(b_t)) \\ &\equiv E(a_t) + E(b_t) \end{aligned} \tag{28}$$

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

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

Furthermore, it is

$$p(\underline{A}_t) \equiv p(c_t) + p(d_t) \equiv (1 - p(A_t)) \tag{30}$$

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

$$\begin{aligned} E(\underline{A}_t) &\equiv A_t \times (1 - p(A_t)) \\ &\equiv A_t \times (p(c_t) + p(d_t)) \\ &\equiv (A_t \times p(c_t)) + (A_t \times p(d_t)) \\ &\equiv E(c_t) + E(d_t) \end{aligned} \tag{31}$$

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

$$\begin{aligned} E(\underline{A}_t) &\equiv A_t \times (1 - p(A_t)) \\ &\equiv (+0+1) \times (1 - p(A_t)) \\ &\equiv (1 - p(A_t)) \\ &\equiv p(c_t) + p(d_t) \end{aligned} \tag{32}$$

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

$$p(B_t) \equiv p(a_t) + p(c_t) \tag{33}$$

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

$$\begin{aligned} E(B_t) &\equiv B_t \times p(B_t) \\ &\equiv B_t \times (p(a_t) + p(c_t)) \\ &\equiv (B_t \times p(a_t)) + (B_t \times p(c_t)) \\ &\equiv E(a_t) + E(c_t) \end{aligned} \tag{34}$$

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

$$\begin{aligned} E\left(B_t\right) &\equiv B_t \times p\left(B_t\right) \\ &\equiv (+0+1) \times p\left(B_t\right) \\ &\equiv p\left(B_t\right) \\ &\equiv p\left(a_t\right) + p\left(c_t\right) \end{aligned} \tag{35}$$

Furthermore, it is

$$p\left(\underline{B}_t\right) \equiv p\left(b_t\right) + p\left(d_t\right) \equiv \left(1 - p\left(B_t\right)\right) \tag{36}$$

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

$$\begin{aligned} E\left(\underline{B}_t\right) &\equiv B_t \times \left(1 - p\left(B_t\right)\right) \\ &\equiv B_t \times \left(p\left(b_t\right) + p\left(d_t\right)\right) \\ &\equiv \left(B_t \times p\left(b_t\right)\right) + \left(B_t \times p\left(d_t\right)\right) \\ &\equiv E\left(b_t\right) + E\left(d_t\right) \end{aligned} \tag{37}$$

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

$$\begin{aligned} E\left(\underline{B}_t\right) &\equiv B_t \times \left(1 - p\left(B_t\right)\right) \\ &\equiv (+0+1) \times \left(1 - p\left(B_t\right)\right) \\ &\equiv \left(1 - p\left(B_t\right)\right) \\ &\equiv p\left(b_t\right) + p\left(d_t\right) \end{aligned} \tag{38}$$

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

$$\begin{aligned} E\left(a_t\right) &\equiv E\left(A_t \wedge B_t\right) \\ &\equiv \left(A_t \times B_t\right) \times p(A_t \wedge B_t) \\ &\equiv \left(A_t \times B_t\right) \times p(a_t) \end{aligned} \tag{39}$$

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

$$\begin{aligned} E\left(a_t\right) &\equiv E\left(A_t \wedge B_t\right) \\ &\equiv \left(A_t \times B_t\right) \times p(A_t \wedge B_t) \\ &\equiv \left((+0+1) \times (+0+1)\right) \times p(A_t \wedge B_t) \\ &\equiv p(A_t \wedge B_t) \\ &\equiv p\left(a_t\right) \end{aligned} \tag{40}$$

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

$$\begin{aligned} E\left(b_t\right) &\equiv E\left(A_t \wedge \neg B_t\right) \\ &\equiv \left(A_t \times \neg B_t\right) \times p(A_t \wedge \neg B_t) \\ &\equiv \left(A_t \times \neg B_t\right) \times p(b_t) \end{aligned} \tag{41}$$

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

$$\begin{aligned} E(b_t) &\equiv E(A_t \wedge \neg B_t) \\ &\equiv (A_t \times \neg B_t) \times p(A_t \wedge \neg B_t) \\ &\equiv ((+0+1) \times (+0+1)) \times p(A_t \wedge \neg B_t) \\ &\equiv p(A_t \wedge \neg B_t) \\ &\equiv p(b_t) \end{aligned} \tag{42}$$

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

$$\begin{aligned} E(c_t) &\equiv E(\neg A_t \wedge B_t) \\ &\equiv (\neg A_t \wedge B_t) \times p(\neg A_t \wedge B_t) \\ &\equiv (\neg A_t \wedge B_t) \times p(c_t) \end{aligned} \tag{43}$$

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

$$\begin{aligned} E(c_t) &\equiv E(\neg A_t \wedge B_t) \\ &\equiv (\neg A_t \times B_t) \times p(\neg A_t \wedge B_t) \\ &\equiv ((+0+1) \times (+0+1)) \times p(\neg A_t \wedge B_t) \\ &\equiv p(\neg A_t \wedge B_t) \\ &\equiv p(c_t) \end{aligned} \tag{44}$$

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

$$\begin{aligned} E(d_t) &\equiv E(\neg A_t \times \neg B_t) \\ &\equiv (\neg A_t \times \neg B_t) \times p(\neg A_t \wedge \neg B_t) \\ &\equiv (\neg A_t \times \neg B_t) \times p(d_t) \end{aligned} \tag{45}$$

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

$$\begin{aligned} E(d_t) &\equiv E(\neg A_t \wedge \neg B_t) \\ &\equiv (\neg A_t \times \neg B_t) \times p(\neg A_t \wedge \neg B_t) \\ &\equiv ((+0+1) \times (+0+1)) \times p(\neg A_t \wedge \neg B_t) \\ &\equiv p(\neg A_t \wedge \neg B_t) \\ &\equiv p(d_t) \end{aligned} \tag{46}$$

In general, it is

$$p(a_t) + p(b_t) + p(c_t) + p(d_t) \equiv +1 \tag{47}$$

Table 5 provide us with an overview of the definitions above.

In our understanding, it is

$$p(B_t) + p(\Lambda_t) \equiv p(a_t) + p(c_t) + p(\Lambda_t) \equiv p(a_t) + p(b_t) \equiv p(A_t) \tag{48}$$

Table 5. 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

or

$$p(c_t) + p(\Lambda_t) \equiv p(b_t) \tag{49}$$

Under conditions of Einstein's general theory of relativity, Λ denotes the Einstein cosmological (Einstein, 1917) 'constant '.

2.4.3. 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

$$p(X_t = k) \equiv \binom{n}{k} \cdot p^k \cdot q^{n-k} \tag{50}$$

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

$$p(X_t \leq k) \equiv 1 - p(X_t > k) \equiv \sum_{t=0}^{k} \binom{n}{t} \cdot p^t \cdot q^{n-t} \tag{51}$$

or as

$$p(X_t > k) \equiv 1 - p(X_t \leq k) \equiv 1 - \sum_{t=0}^{k} \binom{n}{t} \cdot p^t \cdot q^{n-t} \tag{52}$$

Furthermore, it is

$$p(X_t < k) \equiv 1 - p(X_t \geq k) \equiv \sum_{t=0}^{k-1} \binom{n}{t} \cdot p^t \cdot q^{n-t} \tag{53}$$

or

$$p(X_t \geq k) \equiv 1 - p(X_t < k) \equiv 1 - \sum_{t=0}^{k-1} \binom{n}{t} \cdot p^t \cdot q^{n-t} \tag{54}$$

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

$$p\left(X_{\mathrm{t}}=k\right)\equiv p\cdot q^{k-1} \tag{55}$$

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

$$p\left(X_{\mathrm{t}}=r\right)\equiv\binom{k+r-1}{k-1}p^{k}\cdot q^{r} \tag{56}$$

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

Definition 2.12 (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, 2022c) as

$$\sigma\left(X_{\mathrm{t}}\right)^{2}\equiv N\times N\times p\left(X_{\mathrm{t}}\right)\times\left(1-p\left(X_{\mathrm{t}}\right)\right) \tag{57}$$

Definition 2.13 (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

$$\begin{aligned}A&=N\times E\left(A_{\mathrm{t}}\right)\\&\equiv N\times\left(A_{\mathrm{t}}\times p\left(A_{\mathrm{t}}\right)\right)\\&\equiv N\times\left(p\left(A_{\mathrm{t}}\right)+p\left(B_{\mathrm{t}}\right)\right)\\&\equiv N\times p\left(A_{\mathrm{t}}\right)\end{aligned} \tag{58}$$

and

$$\begin{aligned}B&=N\times E\left(B_{\mathrm{t}}\right)\\&\equiv N\times\left(B_{\mathrm{t}}\times p\left(B_{\mathrm{t}}\right)\right)\\&\equiv N\times\left(p\left(A_{\mathrm{t}}\right)+p\left(c_{\mathrm{t}}\right)\right)\\&\equiv N\times p\left(B_{\mathrm{t}}\right)\end{aligned} \tag{59}$$

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

$$a\equiv N\times\left(E\left(A_{\mathrm{t}}\right)\right)\equiv N\times\left(p\left(A_{\mathrm{t}}\right)\right) \tag{60}$$

and

$$b \equiv N \times (E(B_t)) \equiv N \times (p(B_t)) \tag{61}$$

and

$$c \equiv N \times (E(c_t)) \equiv N \times (p(c_t)) \tag{62}$$

and

$$d \equiv N \times (E(d_t)) \equiv N \times (p(d_t)) \tag{63}$$

and

$$a+b+c+d \equiv A+\underline{A} \equiv B+\underline{B} \equiv N \tag{64}$$

Table 6 provide us again an overview of a two by two table of Binomial random variables.

Table 6. 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

2.4.4. Independence

Definition 2.14 (Independence).

2.4.5. Independence

Definition 2.15 (Independence).

The philosophical, mathematical(Kolmogoroff, Andreĭ Nikolaevich, 1933) and physical(Einstein, 1948) et cetera concept of independence is of fundamental(Kolmogoroff, Andreĭ Nikolaevich, 1933) importance in (natural) sciences as such. Therefore, it is appropriate to investigate the concept of independence as completely as possible. In fact, de Moivre sums it up in his book The Doctrine of Chances (see also Moivre, 1718). "Two Events are **independent**, when they have no connexion one with the other, and that the happening of one neither forwards nor obstructs the happening of the other. Two events are **dependent**, when they are so connected together as that the Probability of either's happening is alter'd by the happening of the other. "(see also Moivre, 1756, p. 6) We should consider Kolmogorov's position on independence before the mind's eye too. "The concept of mutual independence of two or more experiments holds, in a certain sense, a central position in the theory of probability."(see also Kolmogorov, Andreĭ Nikolaevich, 1950, p. 8) Furthermore, it is insightful to recall even 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 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. De Moivre brings it to the point. "From what has been said, it follows, that if a Fraction expresses the Probability of an Event, and another Fraction the Probability of another Event, and those two Events are independent ; the Probability that both those Events will Happen, will be the Product of those two Fractions."(see also Moivre, 1718, p. 4). Mathematically, in terms of probability theory, independence (Kolmogoroff, Andreĭ Nikolaevich, 1933) of events at the same (period of) time (i.e. Bernoulli trial) t is defined as

$$\begin{aligned} p(A_t \wedge B_t) &\equiv p(A_t) \times p(B_t) \equiv p(a_t) \\ &\equiv \frac{\sum_{t=1}^{N} (A_t \wedge B_t)}{N} \equiv \frac{N \times (p(a_t))}{N} \equiv 1 - p(A_t \mid B_t) \equiv 1 - p(A_t \uparrow B_t) \end{aligned} \tag{65}$$

while $p(A_t \cap B_t)$ is the joint probability of the events A_t and B_t at a same Bernoulli trial t, $p(A_t)$ is the probability of an event A_t at a same Bernoulli trial t, and $p(B_t)$ is the probability of an event B_t at a same Bernoulli trial t. With respect to a two-by-two table , **under conditions of independence**, it is

$$p(b_t) \equiv p(A_t) \times p(\underline{B}_t) \tag{66}$$

or

$$p(c_t) \equiv p(\underline{A}_t) \times p(B_t) \tag{67}$$

and

$$p(d_t) \equiv p(\underline{A}_t) \times p(\underline{B}_t) \tag{68}$$

Example. 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). Thus far, as a result of the thoughts before, 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)? Meanwhile, this question is more or less already answered 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. It is remarkable that **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.

2.4.6. Dependence

Definition 2.16 (Dependence).

Whilst it may be true that the occurrence of an event A_t does not affect the occurrence of an other event B_t the contrary is of no minor importance. Under these other conditions, events, trials and random variables et cetera are dependent on each other too. The dependence of events (Barukčić, 1989, p. 57-61) is defined as

$$p\left(\underbrace{A_t \wedge B_t \wedge C_t \wedge \dots}_{n \text{ random variables}}\right) \equiv \sqrt[n]{\underbrace{p\left(A_t\right) \times p\left(B_t\right) \times p\left(C_t\right) \times \dots}_{n \text{ random variables}}} \tag{69}$$

2.4.7. Sensitivity and specificity

Definition 2.17 (Sensitivity and specificity)**.**

A (medical) test should measure what is supposed to measure. However, the extent to which a test measures what it is supposed to measure varies and is seldom equal to 100 %. In other words, it is necessary to check once and again the accuracy or the validity of a test, we have to fight it out in detail. In clinical practice, the concept of sensitivity and specificity is commonly used to quantify the diagnostic ability of a (medical) test. Sensitivity and specificity were introduced by the American [11] , [12] , [13] , [14] biostatistician Jacob Yerushalmy (see also Yerushalmy, 1947) in the year 1947. The interior logic of sensitivity and specificity is best illustrated using a conventional two- by-two (2 x 2) table (see table 7).

Table 7. Sensitivity and specificity

		Disease B_t		
		present	absent	
Test	positive	a (true positive)	b (false positive)	A
A_t	negative	c (false negative)	d (true negative)	$\underline{A}$
		B	$\underline{B}$	N

The ability of a positive test (A_t) to correctly classify an individual as diseased (B_t) is defined as the proportion of true positives that are correctly identified by the test (a) divided by the individuals being truly diseased (B_t). In general, sensitivity follows as

$$Sensitivity\,(A \mid B) \equiv p\,(a \mid B) \equiv \frac{a}{B} \tag{70}$$

The specificity of a test is the ability of a negative test ($\underline{A}_t$) to correctly classify an individual as not diseased ($\underline{B}_t$ and is defined as the proportion of true negative that are correctly identified by the test (d) divided by the individuals being truly not diseased ($\underline{B}_t$). In general, specificity is given by the equation

$$Specificity\,(\underline{A},\underline{B}) \equiv p\,(d \mid \underline{B}) \equiv \frac{d}{\underline{B}} \tag{71}$$

The positive predictive value (PPV) is defined as

$$PPV\,(A,B) \equiv \frac{a}{a+b} \tag{72}$$

[11] Yerushalmy Jacob. Statistical problems in assessing methods of medical diagnosis, with special reference to X-ray techniques. Public Health Rep. 1947 Oct 3;62(40):1432-49. PMID: 20340527.

[12] Galen RS, Gambino SR. Beyond normality-the predictive value and efficiency of medical diagnosis. New York: NY:Wiley; 1975.

[13] Altman DG, Bland JM. Diagnostic tests. 1: Sensitivity and specificity. BMJ. 1994 Jun 11;308(6943):1552. doi: 10.1136/bmj.308.6943.1552. PMID: 8019315; PMCID: PMC2540489.

[14] Parikh R, Mathai A, Parikh S, Chandra Sekhar G, Thomas R. Understanding and using sensitivity, specificity and predictive values. Indian J Ophthalmol. 2008 Jan-Feb;56(1):45-50. doi: 10.4103/0301-4738.37595. PMID: 18158403; PMCID: PMC2636062.

The negative predictive value (NPV) is defined as

$$NPV\,(A,B) \equiv \frac{d}{c+d} \tag{73}$$

Example.

The importance of sensitivity and specificity in any research should certainly not be underestimated. However, it is essential not to lose sight of the major advantages and limitations [15] of these measures. In the following, in order to avoid misconceptions about sensitivity, specificity et cetera, let us consider a test with a sensitivity of 95 % and a specificity of 95 %. A two-by-two table is used as an illustration (see table 8).

Table 8. Sensitivity and specificity

		Disease B_t		
		present	absent	
Test	positive	95	5	100
A_t	negative	5	95	100
		100	100	200

Sensitivity is calculated as

$$Sensitivity\,(A \mid B) \equiv p\,(a \mid B) \equiv 100 \times \frac{a}{B} \equiv \frac{95}{100} \equiv 95\% \tag{74}$$

There are at least two kinds of medical tests, diagnostic tests and screening tests. Depending on the type of medical test, there are other logical implications. A screening test should correctly identify all people who suffer from a certain disease or all people with a certain outcome. Therefore, the sensitivity of a screening test should be at best 100 %. Under these conditions, we obtain **without** positive test **no** disease/outcome present. However, confusion should be avoided with regard to the adequacy and usefulness of the sensitivity of a screening test. The sensitivity of a test does not take into account events which are false positive (b) or which are true negative (d), the meaning of these events is ignored completely by sensitivity. Therefore, sensitivity is blind on one eye since its inception and underestimates the extent to which a screening test is able to identify the likely presence of a condition of interest. We calculated a 95 % sensitivity while the true possibility of the test to detect a disease is (see table 8)

$$SINE\,(A,B) \equiv 100 \times \frac{a+b+d}{N} \equiv \frac{95+5+95}{200} \equiv 97.5\% \tag{75}$$

In a way similar to sensitivity, specificity is not much better. Diagnostic tests are able to identify people who do not have a certain condition. Specificity is calculated as

$$Specificity\,(\underline{A} \mid \underline{B}) \equiv p\,(d \mid \underline{B}) \equiv 100 \times \frac{d}{\underline{B}} \equiv \frac{95}{100} \equiv 95\% \tag{76}$$

[15] Trevethan R. Sensitivity, Specificity, and Predictive Values: Foundations, Pliabilities, and Pitfalls in Research and Practice. Front Public Health. 2017 Nov 20;5:307. doi: 10.3389/fpubh.2017.00307. PMID: 29209603; PMCID: PMC5701930.

However, specificity does not take into account any individuals who suffer from a disease, who do have the condition and is well-known for being imperfect because of this fact too. Specificity underestimates the possibility of a diagnostic test to detect a disease. Above, the specificity has been calculated as being 95 %. In point of fact, the ability of the test to detect a disease or the relationship **if** test positive **then** disease present is much better and has to be calculated as (see table 8)

$$IMP(A,B) \equiv \frac{a+c+d}{N} \equiv \frac{95+5+95}{200} \equiv 97.5\% \tag{77}$$

As can be seen, the test detected the disease in 97.5 % while specificity allows only 95 %. How valuable is such a measure epistemologicallly? Measures like sensitivity and specificity are blurring of the issue, do risk leading us astray and disorient us systematically again and again. These measures should be abandoned.

2.4.8. Odds ratio (OR)

Definition 2.18 (Odds ratio (OR))**.**

Odds ratios as an appropriate measure for estimating the relative risk have become widely used in medical reports of case-control studies. The 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 related 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 9. The odds' ratio (OR) is defined as

Table 9. 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

$$\begin{aligned} OR(A_t, B_t) &\equiv \left(\frac{a_t}{b_t}\right) / \left(\frac{c_t}{d_t}\right) \\ &\equiv \left(\frac{a_t \times d_t}{b_t \times c_t}\right) \end{aligned} \tag{78}$$

Remark 2.1. *Odds ratios 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. 78. 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. 78. 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.

2.4.9. Relative risk (RR)

2.4.9.1. Relative risk (RR_{nc})

Definition 2.19 (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(Barukčić, 2021d) of them. In general, relative risk RR_{nc}, which provides some evidence of a necessary condition, is defined as

$$\begin{aligned} RR(A_t,B_t)_{nc} &\equiv \frac{\frac{p(a_t)}{p(A_t)}}{\frac{p(c_t)}{p(NotA_t)}} \\ &\equiv \frac{p(a_t)\times p(NotA_t)}{p(c_t)\times p(A_t)} \\ &\equiv \frac{N\times p(a_t)\times N\times p(NotA_t)}{N\times p(c_t)\times N\times p(A_t)} \\ &\equiv \frac{a_t\times (NotA_t)}{c_t\times A_t} \\ &\equiv \frac{EER\,(A_t,B_t)}{CER\,(A_t,B_t)} \end{aligned} \tag{79}$$

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.

2.4.9.2. Relative risk (RR (sc))

Definition 2.20 (Relative risk (RR (sc)))**.**

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

$$\begin{aligned} RR(A_t,B_t)_{sc} &\equiv \frac{\frac{p(a_t)}{p(B_t)}}{\frac{p(b_t)}{p(NotB_t)}} \\ &\equiv \frac{p(a_t)\times p(NotB_t)}{p(b_t)\times p(B_t)} \\ &\equiv \frac{N\times p(a_t)\times N\times p(NotB_t)}{N\times p(b_t)\times N\times p(B_t)} \\ &\equiv \frac{a_t\times (NotB_t)}{b_t\times B_t} \\ &\equiv \frac{OPR\,(A_t,B_t)}{CPR\,(A_t,B_t)} \end{aligned} \tag{80}$$

2.4.9.3. Relative risk reduction (RRR)

Definition 2.21 (Relative risk reduction (RRR))**.**

$$\begin{aligned} RRR\,(A_t,B_t) &\equiv \frac{CER\,(A_t,B_t)-EER\,(A_t,B_t)}{CER\,(A_t,B_t)} \\ &= 1-RR(A_t,B_t) \end{aligned} \tag{81}$$

2.4.9.4. Vaccine efficacy (VE)

Definition 2.22 (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.

$$\begin{aligned} VE\,(A_t,B_t) &\equiv 100\times (1-RR\,(A_t,B_t)) \\ &\equiv 100\times \left(\frac{CER\,(A_t,B_t)-EER\,(A_t,B_t)}{CER\,(A_t,B_t)}\right) \end{aligned} \tag{82}$$

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.

2.4.9.5. Experimental event rate (EER)

Definition 2.23 (Experimental event rate (EER))**.**

$$EER\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)\equiv\frac{p(a_{\mathrm{t}})}{p(A_{\mathrm{t}})}=\frac{a_{\mathrm{t}}}{a_{\mathrm{t}}+b_{\mathrm{t}}} \tag{83}$$

Definition 2.24 (Control event rate (CER))**.**

$$CER\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)\equiv\frac{p(c_{\mathrm{t}})}{p(\underline{A}_{\mathrm{t}})}=\frac{c_{\mathrm{t}}}{c_{\mathrm{t}}+d_{\mathrm{t}}} \tag{84}$$

2.4.9.6. Absolute risk reduction (ARR)

Definition 2.25 (Absolute risk reducation (ARR))**.**

$$\begin{aligned} ARR\left(A_{\mathrm{t}},B_{\mathrm{t}}\right) &\equiv \frac{p(c_{\mathrm{t}})}{p(\underline{A}_{\mathrm{t}})}-\frac{p(a_{\mathrm{t}})}{p(A_{\mathrm{t}})} \\ &= \frac{c_{\mathrm{t}}}{c_{\mathrm{t}}+d_{\mathrm{t}}}-\frac{a_{\mathrm{t}}}{a_{\mathrm{t}}+b_{\mathrm{t}}} \\ &= CER\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)-EER\left(A_{\mathrm{t}},B_{\mathrm{t}}\right) \end{aligned} \tag{85}$$

2.4.9.7. Absolute risk increase (ARI)

Definition 2.26 (Absolute risk increase (ARI))**.**

$$\begin{aligned} ARI\left(A_{\mathrm{t}},B_{\mathrm{t}}\right) &\equiv \frac{p(a_{\mathrm{t}})}{p(A_{\mathrm{t}})}-\frac{p(c_{\mathrm{t}})}{p(\underline{A}_{\mathrm{t}})} \\ &= EER\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)-CER\left(A_{\mathrm{t}},B_{\mathrm{t}}\right) \end{aligned} \tag{86}$$

2.4.9.8. Number needed to treat (NNT)

Definition 2.27 (Number needed to treat (NNT))**.**

$$NNT\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)\equiv\frac{1}{CER\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)-EER\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)} \tag{87}$$

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.

2.4.9.9. Number needed to harm (NNH)

Definition 2.28 (Number needed to harm (NNH))**.**

$$NNH\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)\equiv\frac{1}{EER\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)-CER\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)} \tag{88}$$

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.

2.4.9.10. Outcome prevalence rate (OPR)

Definition 2.29 (Outcome prevalence rate (OPR))**.**

$$OPR\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)\equiv\frac{p(a_{\mathrm{t}})}{p(B_{\mathrm{t}})}=\frac{a_{\mathrm{t}}}{a_{\mathrm{t}}+c_{\mathrm{t}}} \tag{89}$$

2.4.9.11. Control prevalence rate (CPR)

Definition 2.30 (Control prevalence rate (CPR))**.**

$$CPR\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)\equiv\frac{p(b_{\mathrm{t}})}{p(\underline{B}_{\mathrm{t}})}=\frac{b_{\mathrm{t}}}{b_{\mathrm{t}}+d_{\mathrm{t}}} \tag{90}$$

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.

2.4.9.12. Absolute prevalence reduction (APR)

Definition 2.31 (Absolute prevalence reduction (APR))**.**

$$APR\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) \equiv CPR\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) - OPR\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) \tag{91}$$

2.4.9.13. Absolute prevalence increase (API)

Definition 2.32 (Absolute prevalence increase (API))**.**

$$API\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) \equiv OPR\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) - CPR\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) \tag{92}$$

2.4.9.14. Relative prevalence reduction (RPR)

Definition 2.33 (Relative prevalence reduction (RPR))**.**

$$\begin{aligned} RPR\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) &\equiv \frac{CPR\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) - OPR\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right)}{CPR\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right)} \\ &= 1 - RR(A_{\mathrm{t}}, B_{\mathrm{t}})_{\mathrm{sc}} \end{aligned} \tag{93}$$

2.4.9.15. The index NNS

Definition 2.34 (The index NNS)**.**

$$NNS\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) \equiv \frac{1}{CPR\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) - OPR\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right)} \tag{94}$$

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

2.4.9.16. The index NNI

Definition 2.35 (The index NNI)**.**

$$NNI\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) \equiv \frac{1}{OPR\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) - CPR\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right)} \tag{95}$$

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

2.4.10. Index of relationship (IOR)

Definition 2.36 (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 [16] , is defined as

$$\begin{aligned} IOR(A_t, B_t) &\equiv \left(\frac{p(A_t \wedge B_t)}{p(B_t) \times p(A_t)} \right) - 1 \\ &\equiv \left(\frac{p(a_t)}{p(B_t) \times p(A_t)} \right) - 1 \\ &\equiv \left(\left(\frac{N \times N \times p(a_t)}{N \times p(B_t) \times N \times p(A_t)} \right) - 1 \right) \\ &\equiv \left(\left(\frac{N \times a}{A \times B} \right) - 1 \right) \end{aligned} \tag{96}$$

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.

[16] Barukčić, Ilija. (2021). Index of relationship. Causation, 16(8), 5–37. https://doi.org/10.5281/zenodo.5163179

2.5. Conditions

2.5.1. Exclusion relationship

Definition 2.37 (**Exclusion relationship [*EXCL*]**).

Mathematically, the exclusion(see also Barukčić, 2021a) relationship [17] (EXCL), denoted by $p(A_t \mid B_t)$ in terms of statistics and probability theory, is defined(see also Barukčić, 1989, p. 68-70) as

$$\begin{aligned} p(A_t \mid B_t) &\equiv p(A_t \uparrow B_t) \\ &\equiv p(b_t) + p(c_t) + p(d_t) \\ &\equiv \frac{N \times (p(b_t) + p(c_t) + p(d_t))}{N} \\ &\equiv \frac{\sum_{t=1}^{N} (\underline{A}_t \vee \underline{B}_t)}{N} \equiv \frac{b+c+d}{N} \\ &\equiv \frac{b+\underline{A}}{N} \\ &\equiv \frac{c+\underline{B}}{N} \\ &\equiv +1 \end{aligned} \tag{97}$$

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 10).

Table 10. 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*

[17] Barukčić, Ilija. (2021). Mutually exclusive events. Causation, 16(11), 5–57. https://doi.org/10.5281/zenodo.5746415

group versus 162 in the placebo group. The exclusion relationship can be calculated as follows.

$$\begin{aligned} p\left(Vaccine : BNT162b2 \mid COVID-19(infection)\right) &\equiv p\left(b_t\right)+p\left(c_t\right)+p\left(d_t\right) \\ &\equiv 1-p\left(a_t\right) \\ &\equiv 1-\left(\frac{8}{43538}\right) \\ &\equiv +0,99981625 \end{aligned} \tag{98}$$

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

$$\begin{aligned} p\left(A_{\mathrm{t}} \mid B_{\mathrm{t}}\right) &\equiv p\left(\underline{A}_{\mathrm{t}} \cup \underline{B}_{\mathrm{t}}\right) \\ &\equiv 1-p\left(A_{\mathrm{t}} \cap B_{\mathrm{t}}\right) \\ &\equiv 1-\int_{-\infty}^{A_{\mathrm{t}}} \int_{-\infty}^{B_{\mathrm{t}}} f\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right)\, dA_{\mathrm{t}}\, dB_{\mathrm{t}} \\ &\equiv +1 \end{aligned} \tag{99}$$

while $p\left(A_{\mathrm{t}} \mid B_{\mathrm{t}}\right)$ would denote the cumulative distribution function of random variables and $f\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right)$ is the joint density function.

2.5.2. Observational study and exclusion relationship

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

$$p\left(A_{\mathrm{t}} \mid B_{\mathrm{t}}\right) \equiv p\left(A_{\mathrm{t}} \uparrow B_{\mathrm{t}}\right) \geq 1-\frac{p\left(a_{\mathrm{t}}\right)}{p\left(B_{\mathrm{t}}\right)} \tag{100}$$

2.5.3. Experimental study and exclusion relationship

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

$$p\left(A_{\mathrm{t}} \mid B_{\mathrm{t}}\right) \equiv p\left(A_{\mathrm{t}} \uparrow B_{\mathrm{t}}\right) \geq 1-\frac{p\left(a_{\mathrm{t}}\right)}{p\left(A_{\mathrm{t}}\right)} \tag{101}$$

2.5.4. The goodness of fit test of an exclusion relationship

Definition 2.38 (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

$$\begin{aligned}\tilde{\chi}^2{}_{\text{Calculated}}\left((A_t \mid B_t) \mid A\right) &\equiv \frac{(b-(a+b))^2}{A}+ \\ &\quad \frac{((c+d)-\underline{A})^2}{\underline{A}} \\ &\equiv \frac{a^2}{A}+0 \\ &\equiv \frac{a^2}{A}\end{aligned} \tag{102}$$

or equally as

$$\begin{aligned}\tilde{\chi}^2{}_{\text{Calculated}}\left((A_t \mid B_t) \mid B\right) &\equiv \frac{(c-(a+c))^2}{B}+ \\ &\quad \frac{((b+d)-\underline{B})^2}{\underline{B}} \\ &\equiv \frac{a^2}{B}+0 \\ &\equiv \frac{a^2}{B}\end{aligned} \tag{103}$$

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 $p(A_t \mid B_t)$, in which case the null hypothesis has to be accepted. Yate's (Yates, 1934) continuity correction was not used under these circumstances.

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

Definition 2.39 (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, 2019d) of an exclusion relationship can be calculated as follows.

$$\begin{aligned}pValue_{\text{lt}}\left(A_t \mid B_t\right) &\equiv 1-e^{-(1-p(A_t|B_t))} \\ &\equiv 1-e^{-(a/N)}\end{aligned} \tag{104}$$

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

2.5.6. Neither nor conditions

Definition 2.40 (**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

$$\begin{aligned} p\left(A_t \downarrow B_t\right) &\equiv p\left(d_t\right) \\ &\equiv \frac{N - \sum_{t=1}^{N} \left(A_t \vee B_t\right)}{N} \equiv \frac{\sum_{t=1}^{N} \left(\underline{A}_t \wedge \underline{B}_t\right)}{N} \equiv \frac{N \times \left(p\left(d_t\right)\right)}{N} \\ &\equiv \frac{d}{N} \\ &\equiv +1 \end{aligned} \tag{105}$$

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

Definition 2.41 (**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

$$\begin{aligned} {\tilde{\chi}^2}_{\text{Calculated}}\left(\left(A_t \downarrow B_t\right) \mid A\right) &\equiv \frac{\left(d - \left(c + d\right)\right)^2}{\underline{A}} + \\ &\quad \frac{\left(\left(a + b\right) - A\right)^2}{A} \\ &\equiv \frac{c^2}{\underline{A}} + 0 \end{aligned} \tag{106}$$

or equally as

$$\begin{aligned} {\tilde{\chi}^2}_{\text{Calculated}}\left(\left(A_t \downarrow B_t\right) \mid B\right) &\equiv \frac{\left(d - \left(b + d\right)\right)^2}{\underline{B}} + \\ &\quad \frac{\left(\left(a + c\right) - B\right)^2}{B} \\ &\equiv \frac{b^2}{\underline{B}} + 0 \end{aligned} \tag{107}$$

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

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

Definition 2.42 (The left-tailed p Value of a neither A_t nor B_t condition relationship).

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

$$\begin{aligned} pValue_{\text{lt}}\left(A_t \downarrow B_t\right) &\equiv 1 - e^{-(1-p(A_t \downarrow B_t))} \\ &\equiv 1 - e^{-p(A_t \vee B_t)} \\ &\equiv 1 - e^{-((a+b+c)/N)} \end{aligned} \tag{108}$$

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 11).

Table 11. 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

2.5.9. Necessary condition

Definition 2.43 (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, of Stageira (384-322 B.C.E), 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, of Stageira (384-322 B.C.E), 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, of Stageira (384-322 B.C.E), 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. Among many other issues, the specification of necessary conditions has traditionally been part of the philosopher's investigations of different phenomena. However, 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 re-consider 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 need to 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 such an event. In other words, if a necessary condition (i.e. A_t) is given, an outcome (i.e. B_t) need not to occur. In contrast to a necessary condition, a 'sufficient'condition is the one condition which 'guarantees'that an outcome will take place or will 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 a brain is given ... et cetera, without water 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

$$\begin{aligned} p\left(A_t \leftarrow B_t\right) \equiv p\left(A_t \vee \underline{B}_t\right) &\equiv \frac{\sum_{t=1}^{N}\left(A_t \vee \underline{B}_t\right)}{N} \equiv \frac{\left(A_t \vee \underline{B}_t\right) \times p\left(A_t \vee \underline{B}_t\right)}{\left(A_t \vee \underline{B}_t\right)} \\ &\equiv p\left(a_t\right) + p\left(b_t\right) + p\left(d_t\right) \\ &\equiv \frac{N \times \left(p\left(a_t\right) + p\left(b_t\right) + p\left(d_t\right)\right)}{N} \equiv \frac{E\left(A_t \leftarrow B_t\right)}{N} \\ &\equiv \frac{a+b+d}{N} \equiv \frac{E\left(A_t \vee \underline{B}_t\right)}{N} \\ &\equiv \frac{A+d}{N} \equiv \frac{E\left(A_t \leftarrow B_t\right)}{N} \\ &\equiv \frac{a+\underline{B}}{N} \equiv \frac{E\left(A_t \vee \underline{B}_t\right)}{N} \\ &\equiv +1 \end{aligned} \tag{109}$$

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 12).

A necessary condition A_t is characterised itself by the property that another event B_t will not occur if

Table 12. 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

A_t is not given, if A_t did not occur (Barukčić, 1989, 1997, 2005, 2016b, 2017b,c, 2020a,b,c,d, Barukčić and Ufuoma, 2020). 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

$$\begin{aligned} p\left(A_t \leftarrow B_t\right) &\equiv +1 \\ &\equiv +1 - p\left(c_t\right) \\ &\equiv +1 - p\left(\underline{A}_t \cap B_t\right) \\ &\equiv \left(\int_{-\infty}^{A_t} \int_{-\infty}^{B_t} f\left(A_t, B_t\right) \, dA_t \, dB_t \right) + \left(1 - \int_{-\infty}^{B_t} f\left(B_t\right) \, dB_t \right) \end{aligned} \tag{110}$$

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. If certain conditions are met, then necessary conditions and sufficient conditions are one way or another converses of each other, too. It is

$$p\left(A_t \leftarrow B_t\right) \equiv \underbrace{\left(A_t \vee \underline{B}_t\right)}_{\text{(Necessary condition)}} \equiv \underbrace{\left(\underline{B}_t \vee A_t\right)}_{\text{(Sufficient condition)}} \equiv p\left(B_t \rightarrow A_t\right) \tag{111}$$

These relationships are illustrated by the following tables.

Table 13. Without A_t no B_t

		B_t		
		TRUE	FALSE	
A_t	TRUE	a_t	b_t	A_t
	FALSE	$c_t = 0$	d_t	$\underline{A}_t$
		B_t	$\underline{B}_t$	+1

Table 14. If B_t then A_t

		A_t		
		TRUE	FALSE	
B_t	TRUE	a_t	$c_t = 0$	B_t
	FALSE	b_t	d_t	$\underline{B}_t$
		A_t	$\underline{A}_t$	+1

There are circumstances under which

$$p\left(A_t \leftarrow B_t\right) \equiv \underbrace{\left(A_t \vee \underline{B}_t\right)}_{\text{(Nessessary condition)}} \equiv \underbrace{\left(\underline{A}_t \vee B_t\right)}_{\text{(Sufficient condition)}} \equiv p\left(A_t \rightarrow B_t\right) \tag{112}$$

However, equation 111 does not imply the relationship of equation 112 under any circumstances.

Example I.

A wax candle is characterised by various properties, but is also subject to certain conditions. **Without** sufficient amounts of gaseous oxygen **no** burning wax candle, gaseous oxygen is a necessary condition of a burning candle. However, the converse relationship **if** burning wax candle, **then** sufficient amounts of gaseous oxygen are given is is at the same (period of) time t / Bernoulli trial t true. The following tables are illustrating these relationships.

Table 15. Without gaseous oxygen no burning candle

		Burning candle		
		TRUE	FALSE	
Gaseous oxygen	TRUE	a_t	b_t	A_t
	FALSE	$c_t = 0$	d_t	$\underline{A_t}$
		B_t	$\underline{B_t}$	+1

Table 16. If burning candle then gaseous oxygen

		Gaseous oxygen		
		TRUE	FALSE	
Burning candle	TRUE	a_t	$c_t = 0$	B_t
	FALSE	b_t	d_t	$\underline{B_t}$
		A_t	$\underline{A_t}$	+1

Example II.

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.

Example III.

Another different aspect of a necessary condition relationship is appropriate to be focused upon here. As a direct consequence of a necessary condition **without** sufficient amounts of gaseous oxygen **no** burning wax candle is a special case of an exclusion relationship. The absence of sufficient amounts of gaseous oxygen A_t excludes (see Barukčić, 2021a) a burning wax candle B_t. Thus far, if we want to stop the burning of a wax candle, we would have to significantly reduce the amounts of gaseous oxygen A_t. Under these conditions, a wax candle will stop burning. The following tables (table 17 and table 18) may illustrate this aspect of a necessary condition in more detail.

Table 17. Without gaseous oxygen no burning candle

		Burning candle		
		TRUE	FALSE	
Gaseous oxygen	TRUE	a_t	b_t	A_t
	FALSE	$c_t = 0$	d_t	$\underline{A_t}$
		B_t	$\underline{B_t}$	+1

Table 18. Absent gaseous oxygen excludes burning wax candle

		Burning candle		
		TRUE	FALSE	
Gaseous oxygen	FALSE	$c_t = 0$	d_t	B_t
	TRUE	a_t	b_t	$\underline{B_t}$
		A_t	$\underline{A_t}$	+1

The necessary condition relationship follows approximately (see Barukčić, 2022b) as

$$p\left(A_{\mathrm{t}} \leftarrow B_{\mathrm{t}}\right) \geq 1 - \frac{p\left(c_{\mathrm{t}}\right)}{p\left(B_{\mathrm{t}}\right)} \tag{113}$$

and as

$$p\left(A_{\mathrm{t}} \leftarrow B_{\mathrm{t}}\right) \geq 1 - \frac{p\left(c_{\mathrm{t}}\right)}{p\left(\underline{A}_{\mathrm{t}}\right)} \tag{114}$$

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

Definition 2.44 (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 $\mathrm{p}(\mathrm{A_t} \leftarrow \mathrm{B_t})$ 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

$$\begin{aligned} {\tilde{\chi}^2}_{\text{Calculated}}\left(A_{\mathrm{t}} \leftarrow B_{\mathrm{t}} \mid B\right) &\equiv \frac{\left(a-(a+c)\right)^2}{B} + \\ &\quad \frac{\left((b+d)-\underline{B}\right)^2}{\underline{B}} \\ &\equiv \frac{c^2}{B} + 0 \\ &\equiv \frac{c^2}{B} \end{aligned} \tag{115}$$

or equally as

$$\begin{aligned} {\tilde{\chi}^2}_{\text{Calculated}}\left(A_{\mathrm{t}} \leftarrow B_{\mathrm{t}} \mid \underline{A}\right) &\equiv \frac{\left(d-(c+d)\right)^2}{\underline{A}} + \\ &\quad \frac{\left((a+b)-A\right)^2}{A} \\ &\equiv \frac{c^2}{\underline{A}} + 0 \\ &\equiv \frac{c^2}{\underline{A}} \end{aligned} \tag{116}$$

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.

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

Definition 2.45 (**The left-tailed p Value of the conditio sine qua non relationship**).

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

$$\begin{aligned} pValue_{\mathrm{lt}}\left(A_{\mathrm{t}} \leftarrow B_{\mathrm{t}}\right) &\equiv 1-e^{-(1-p(A_{\mathrm{t}} \leftarrow B_{\mathrm{t}}))} \\ &\equiv 1-e^{-(c/N)} \end{aligned} \tag{117}$$

2.5.12. Sufficient condition

Definition 2.46 (**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

$$\begin{aligned} p\left(A_{\mathrm{t}} \rightarrow B_{\mathrm{t}}\right) \equiv p\left(\underline{A}_{\mathrm{t}} \vee B_{\mathrm{t}}\right) &\equiv \frac{\sum_{t=1}^{N}\left(\underline{A}_{\mathrm{t}} \vee B_{\mathrm{t}}\right)}{N} \equiv \frac{\left(\underline{A}_{\mathrm{t}} \vee B_{\mathrm{t}}\right) \times p\left(\underline{A}_{\mathrm{t}} \vee B_{\mathrm{t}}\right)}{\left(\underline{A}_{\mathrm{t}} \vee B_{\mathrm{t}}\right)} \\ &\equiv p\left(a_{\mathrm{t}}\right)+p\left(c_{\mathrm{t}}\right)+p\left(d_{\mathrm{t}}\right) \\ &\frac{N \times\left(p\left(a_{\mathrm{t}}\right)+p\left(c_{\mathrm{t}}\right)+p\left(d_{\mathrm{t}}\right)\right)}{N} \\ &\equiv \frac{a+c+d}{N} \equiv \frac{E\left(\underline{A}_{\mathrm{t}} \vee B_{\mathrm{t}}\right)}{N} \\ &\equiv \frac{B+d}{N} \equiv \frac{E\left(A_{\mathrm{t}} \rightarrow B_{\mathrm{t}}\right)}{N} \\ &\equiv \frac{a+\underline{A}}{N} \\ &\equiv +1 \end{aligned} \tag{118}$$

In general, 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 19). There are circumstances, where several different events might be necessary at the same time in order to determine a compound sufficient condition relationship. Equation 119 illustrates this case in more detail.

$$\begin{aligned} p\left(\left(\left({}_1X_{\mathrm{t}} \wedge {}_2X_{\mathrm{t}} \wedge {}_3X_{\mathrm{t}} \wedge \cdots\right) \wedge A_{\mathrm{t}}\right) \rightarrow B_{\mathrm{t}}\right) &\equiv p\left(\underline{\left(\left({}_1X_{\mathrm{t}} \wedge {}_2X_{\mathrm{t}} \wedge {}_3X_{\mathrm{t}} \wedge \cdots\right) \wedge A_{\mathrm{t}}\right)} \vee B_{\mathrm{t}}\right) \\ &\equiv \frac{\sum_{t=1}^{N}\left(\underline{\left(\left({}_1X_{\mathrm{t}} \wedge {}_2X_{\mathrm{t}} \wedge {}_3X_{\mathrm{t}} \wedge \cdots\right) \wedge A_{\mathrm{t}}\right)} \vee B_{\mathrm{t}}\right)}{N} \\ &\equiv +1 \end{aligned} \tag{119}$$

Again, taking into account Kolmogorov's definition of an n-dimensional probability density (see also Kolmogorov, Andreĭ Nikolaevich, 1950, p. 26) of random variables $\mathrm{A_t}$, $\mathrm{B_t}$ et cetera at the (period of)

time t, we obtain

$$\begin{aligned} p\left(A_{\mathrm{t}} \rightarrow B_{\mathrm{t}}\right) &\equiv +1 \\ &\equiv +1-p\left(b_{\mathrm{t}}\right) \\ &\equiv +1-p\left(A_{\mathrm{t}} \cap \underline{B}_{\mathrm{t}}\right) \\ &\equiv \left(\int_{-\infty}^{A_{\mathrm{t}}} \int_{-\infty}^{B_{\mathrm{t}}} f\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right)\, dA_{\mathrm{t}}\, dB_{\mathrm{t}}\right)+\left(1-\int_{-\infty}^{A_{\mathrm{t}}} f\left(A_{\mathrm{t}}\right)\, dA_{\mathrm{t}}\right) \end{aligned} \tag{120}$$

while $p\left(A_{\mathrm{t}} \rightarrow B_{\mathrm{t}}\right)$ would denote the cumulative distribution function of random variables of a sufficient condition. Another adequate formulation of a sufficient condition is possible too.

Table 19. Sufficient condition.

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

$$p\left(A_t \rightarrow B_t\right)+p\left(R_t \wedge B_t\right) \equiv +1 \tag{121}$$

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.

The approximate (see Barukčić, 2022a) value of the material implication is given as

$$p\left(A_{\mathrm{t}} \rightarrow B_{\mathrm{t}}\right) \geq 1-\frac{p\left(b_{\mathrm{t}}\right)}{p\left(A_{\mathrm{t}}\right)} \tag{122}$$

and alternatively as

$$p\left(A_{\mathrm{t}} \rightarrow B_{\mathrm{t}}\right) \geq 1-\frac{p\left(b_{\mathrm{t}}\right)}{p\left(\underline{B}_{\mathrm{t}}\right)} \tag{123}$$

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

Definition 2.47 (**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

$$\begin{aligned} {\tilde{\chi}^2}_{\text{Calculated}}\left(A_t \rightarrow B_t \mid A\right) &\equiv \frac{\left(a-(a+b)\right)^2}{A}+ \\ &\quad \frac{\left((c+d)-\underline{A}\right)^2}{\underline{A}} \\ &\equiv \frac{b^2}{A}+0 \\ &\equiv \frac{b^2}{A} \end{aligned} \tag{124}$$

or equally as

$$\begin{aligned} {\tilde{\chi}^2}_{\text{Calculated}}\left(A_t \rightarrow B_t \mid \underline{B}\right) &\equiv \frac{\left(d-(b+d)\right)^2}{\underline{B}}+ \\ &\quad \frac{\left((a+c)-B\right)^2}{B} \\ &\equiv \frac{b^2}{\underline{B}}+0 \\ &\equiv \frac{b^2}{\underline{B}} \end{aligned} \tag{125}$$

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.

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

Definition 2.48 (**The left-tailed p Value of the conditio per quam relationship**).

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

as follows.

$$\begin{aligned} pValue_{\mathrm{lt}}\left(A_{\mathrm{t}} \rightarrow B_{\mathrm{t}}\right) &\equiv 1-e^{-\left(1-p\left(A_{\mathrm{t}} \rightarrow B_{\mathrm{t}}\right)\right)} \\ &\equiv 1-e^{-(b/N)} \end{aligned} \tag{126}$$

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

2.5.15. Necessary and sufficient conditions

Definition 2.49 (**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

$$\begin{aligned} p\left(A_{\mathrm{t}} \leftrightarrow B_{\mathrm{t}}\right) &\equiv \frac{\sum_{t=1}^{N}\left(\left(A_{\mathrm{t}} \vee \underline{B}_{\mathrm{t}}\right) \wedge \left(\underline{A}_{\mathrm{t}} \vee B_{\mathrm{t}}\right)\right)}{N} \\ &\equiv p\left(a_{\mathrm{t}}\right)+p\left(d_{\mathrm{t}}\right) \\ &\equiv \frac{N \times \left(p\left(a_{\mathrm{t}}\right)+p\left(d_{\mathrm{t}}\right)\right)}{N} \\ &\equiv \frac{a+d}{N} \\ &\equiv +1 \end{aligned} \tag{127}$$

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

Definition 2.50 (**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

$$\begin{aligned} {\tilde{\chi}^2}_{\text{Calculated}}\left(A_{\mathrm{t}} \leftrightarrow B_{\mathrm{t}} \mid A\right) &\equiv \frac{\left(a-(a+b)\right)^2}{A}+ \\ &\quad \frac{d-((c+d))^2}{\underline{A}} \\ &\equiv \frac{b^2}{A}+\frac{c^2}{\underline{A}} \end{aligned} \tag{128}$$

or equally as

$$\begin{aligned}\tilde{\chi}^2{}_{\text{Calculated}}\left(A_{\text{t}} \leftrightarrow B_{\text{t}} \mid B\right) &\equiv \frac{\left(a-(a+c)\right)^2}{B}+ \\ &\quad \frac{d-\left((b+d)\right)^2}{\underline{B}} \\ &\equiv \frac{c^2}{B}+\frac{b^2}{\underline{B}}\end{aligned} \tag{129}$$

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.

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

Definition 2.51 (The left-tailed p Value of a necessary and sufficient condition relationship).

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

$$\begin{aligned}pValue_{\text{lt}}\left(A_{\text{t}} \leftrightarrow B_{\text{t}}\right) &\equiv 1-e^{-(1-p(A_{\text{t}} \leftrightarrow B_{\text{t}}))} \\ &\equiv 1-e^{-((b+c)/N)}\end{aligned} \tag{130}$$

In this context, a low p-value indicates again a statistical significance. Table 20 may provide an overview of the theoretical distribution of a necessary and sufficient condition.

Table 20. Necessary and sufficient condition.

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

2.5.18. Either or conditions

Definition 2.52 (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

$$\begin{aligned} p\left(A_t \succ\!\prec B_t\right) &\equiv \frac{\sum_{t=1}^{N}\left(\left(A_t \wedge \underline{B}_t\right) \vee \left(\underline{A}_t \wedge B_t\right)\right)}{N} \\ &\equiv p\left(b_t\right) + p\left(c_t\right) \\ &\equiv \frac{N \times \left(p\left(b_t\right) + p\left(c_t\right)\right)}{N} \\ &\equiv \frac{b+c}{N} \\ &\equiv +1 \end{aligned} \tag{131}$$

It is $p\left(A_t \succ\!\prec B_t\right) \equiv 1 - p\left(A_t <\!\!\succ B_t\right)$ (see Table 21).

Table 21. 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

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

Definition 2.53 (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

$$\begin{aligned} \tilde{\chi}^2{}_{\text{Calculated}}\left(\left(A_t \succ\!\prec B_t\right) \mid A\right) &\equiv \frac{\left(b-\left(a+b\right)\right)^2}{A} + \\ &\quad \frac{c-\left(\left(c+d\right)\right)^2}{\underline{A}} \\ &\equiv \frac{a^2}{A} + \frac{d^2}{\underline{A}} \end{aligned} \tag{132}$$

or equally as

$$\begin{aligned}\tilde{\chi}^2{}_{\text{Calculated}}\left((A_{\text{t}} \succ\!\prec B_{\text{t}}) \mid B\right) &\equiv \frac{\left(c-(a+c)\right)^2}{B}+ \\ &\quad \frac{b-\left((b+d)\right)^2}{\underline{B}} \\ &\equiv \frac{a^2}{B}+\frac{d^2}{\underline{B}}\end{aligned} \tag{133}$$

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

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

Definition 2.54 (The left-tailed p Value of an either or condition relationship).

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

$$\begin{aligned}pValue_{\text{lt}}\left(A_{\text{t}} \succ\!\prec B_{\text{t}}\right) &\equiv 1-e^{-(1-p(A_{\text{t}}>-<B_{\text{t}}))} \\ &\equiv 1-e^{-((a+d)/N)}\end{aligned} \tag{134}$$

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

2.5.21. 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 20$^{\text{th}}$ 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 epidemiological 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 by various modern authors (Barukčić, 1989, 1997, 2005, 2016b, 2017a,c, Bohr, 1937, Chisholm, 1946, Dempster, 1990, Espejo, 2007, Goodman, 1947, Granger, 1969, Hessen, Johannes, 1928, Hesslow, 1976, 1981, Korch, Helmut, 1965, Lewis, 1974, Lewis, David Kellogg, 1973, Pearl, 2000, Schlick, Friedrich Albert Moritz, 1931, Spohn, 1983, Suppes, 1970, Todd, 1968, 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 2.55 (**Causal relationship k**)**.**

Nonetheless, mathematically, the causal(Barukčić, 2011a,b, 2012) relationship (Barukčić, 1989, 1997, 2005, 2016b, 2017a,c, 2021c) 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

$$\begin{aligned} k\left(U_t, W_t\right) &\equiv \frac{\sigma\left(U_t, W_t\right)}{\sigma\left(U_t\right) \times \sigma\left(W_t\right)} \\ &\equiv \frac{p\left(U_t \wedge W_t\right) - p\left(U_t\right) \times p\left(W_t\right)}{\sqrt[2]{\left(p\left(U_t\right) \times \left(1 - p\left(U_t\right)\right)\right) \times \left(p\left(W_t\right) \times \left(1 - p\left(W_t\right)\right)\right)}} \end{aligned} \tag{135}$$

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 22 illustrates the theoretically possible relationships between a cause and an effect.

Table 22. Sample space and the causal relationship k

		Effect B_t		
		TRUE	FALSE	
Cause A_t	TRUE	$p(a_t)$	$p(b_t)$	$p(U_t)$
	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.

2.5.22. Cause and effect

Definition 2.56 (**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 23 may illustrate this relationship.

Table 23. 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

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

$$(U_t \vee \underline{W}_t) \equiv (\underline{W}_t \vee U_t) \equiv ((U_t \vee \underline{W}_t) \wedge (\underline{W}_t \vee U_t)) \equiv +1 \tag{136}$$

In our everyday words,

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

$$(\underline{U}_t \vee W_t) \equiv (W_t \vee \underline{U}_t) \equiv ((\underline{U}_t \vee W_t) \wedge (W_t \vee \underline{U}_t)) \equiv +1 \tag{137}$$

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

$$(U_t \vee \underline{W}_t) \wedge (\underline{U}_t \vee W_t) \equiv +1 \tag{138}$$

However, I think it necessary to make a clear distinction between a necessary and sufficient condition and the converse relationship (Eq. 136) above.

$$((U_t \vee \underline{W}_t) \wedge (\underline{W}_t \vee U_t)) \neq (U_t \vee \underline{W}_t) \wedge (\underline{U}_t \vee W_t) \tag{139}$$

2.6. Axioms

Whether science needs new and obviously generally valid statements (axioms) which are able to assure the truth of theorems proved from them may remain an unanswered question. In order to be accepted, a new axiom candidate (see Easwaran, 2008) should be at least as simple as possible and logically consistent to enable advances in our knowledge of nature. The importance of axioms is particularly emphasized by Albert Einstein. "**Die wahrhaft großen Fortschritte der Naturerkenntnis sind auf einem der Induktion fast diametral entgegengesetzten Wege entstanden**." (see Einstein, 1919, p. 17). In general, lex identitatis, lex contradictionis and lex negationis have the potential to denote the most simple, the most general and the most far-reaching axioms of science, the foundation of our today's and of our future scientific inquiry.

2.6.1. Axiom I. Lex identitatis

In this context, we define axiom I as the expression

$$+1 = +1 \tag{140}$$

Backed by thousands of years of often bitter human experience, the scientific development has taught us all that human knowledge is relative too. Even if experiments and other suitable proofs are of help to encourage us more and more in our belief of the correctness of a theory, it is difficult to prove the correctness of a theorem or of a theory et cetera once and for all. The challenge for all the science is the need to comply with Einstein's position: **"Niemals aber kann die Wahrheit einer Theorie erwiesen werden. Denn niemals weiß man, daß auch in Zukunft eine Erfahrung bekannt werden wird, die Ihren Folgerungen widerspricht..."** (Einstein, 1919). Albert Einstein's position translated into English: 'But the truth of a theory can never be proven. For one never knows if future experience will contradict its conclusion; and furthermore, there are always other conceptual systems imaginable which might coordinate the very same facts.'Our human experience tells us that everything in life is more or less transitory, and that nothing lasts. As a result of our knowledge and experience, several scientific theories have a glorious past to look back on, but all the glory of such scientific theories might remain in the past if scientist don't continue to innovate. In a word, theories can be refuted by time.

> "No amount of experimentation can ever prove me right;
> **a single experiment can prove me wrong**."
>
> (Albert Einstein according to: Robertson, 1998, p. 114)

In the light of the foregoing, it is clear that appropriate axioms and conclusions derived from the same are a main logical foundation of any 'theory'.

"**Grundgesetz (Axiome)**
und
Folgerungen
zusammen bilden das was man
eine 'Theorie'
nennt. "
(Einstein, 1919)

However, another point is worth being considered again. One single experiment can be enough to refute a whole theory. Albert Einstein's (1879-1955) message translated into English as: *Basic law (axioms) and conclusions together form what is called a 'theory'* has still to get round. However, an axiom as a free creation of the human mind which precedes all science should be like all other axioms, as simple as possible and as self-evident as possible. Historically, Aristotle himself already cited **the law of excluded middle** and **the law of contradiction** as examples of axioms. However, **lex identitatis** is an axiom too, which possess the potential to serve as the most basic and equally the most simple axiom of science. Something which is really just itself is equally different from everything else. In point of fact, is such an equivalence which everything has to itself inherent or must the same be constructed by human mind and consciousness. Can and how can something be **identical with itself** (Förster and Melamed, 2012, Hegel, Georg Wilhelm Friedrich, 1812a, Koch, 1999, Newstadt, 2015) and in the same respect different from itself. An increasingly popular view on identity is the one advocated by Gottfried Wilhelm Leibniz (1646-1716):

"**Chaque chose est ce qu'elle est. Et dans autant d'exemples qu'on voudra**
A est A,
B est B. "
(Leibniz, 1765)

or **A = A**, **B = B** or **+1 = +1**. Exactly in complete compliance with Leibniz, Johann Gottlieb Fichte (1762 - 1814) elaborates on this subject as follows:

"**Each thing is what it is ;**
it has those realities which are posited when it is posited,
(A = A.) "
(Fichte, 1889)

We may usefully (see Barukčić, 2019a), state Russell's position with respect to the identity law as mentioned in his book 'The problems of philosophy ' (see Russell, 1912). In particular, according to Russell,

> "...principles have been singled out by tradition under the name of 'Laws of Thought.' They are as follows:
> (1) **The law of identity**: 'Whatever is,is.
> (2)**The law of contradiction**: 'Nothing can both be and not be.'
> (3) The law of excluded middle: 'Everything must either be or not be.'
> These three laws are samples of self-evident logical principles, but are not really more fundamental or more self-evident than various other similar principles: for instance, the one we considered just now, which states that what follows from a true premise is true. The name 'laws of thought' is also misleading, for what is important is not the fact that we think in accordance with these laws, but the fact that **things behave in accordance with them**; "
>
> (see Russell, 1912, p. 113)

Russell's critique, that we tend too much to focus only on the formal aspects of the 'Laws of Thoughts' with the consequence that "... we thing in accordance with these laws" (see Russell, 1912, p. 113) is justified. Judged solely in terms of this aspect, it is of course necessary to think in accordance with the 'Laws of Thoughts'. But this is not the only aspect of the 'Laws of Thoughts'. The other and may be much more important aspect of these 'Laws of Thoughts'is the fact that quantum mechanical objects or that "... things behave in accordance with them" (see Russell, 1912, p. 113).

2.6.2. Axiom II. Lex contradictionis

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

$$+0 = +1 \tag{141}$$

and equally the most simple form of a contradiction formulated.

Thus far, axiom II is of no minor importance too. Scientist inevitably have false beliefs and make mistakes. In order to prevent scientific results from falling into logical inconsistency or logical absurdity, it is necessary to posses among other the methodological possibility to start a reasoning with a contradiction too. However and in contrast to the way of reasoning with inconsistent premises as proposed by para-consistent logic (Carnielli and Marcos, 2001, da Costa, 1974, 1958, Priest, 1998, Priest et al., 1989, Quesada, 1977), in the absence of technical and other errors of reasoning, the contradiction itself need to be preserved. In other words, **from a contradiction does not anything follows but the contradiction itself** while the theoretical question is indeed justified "What is so Bad about Contradictions? " (Priest, 1998). Historically, **the principle of (deductive) explosion**, coined by 12th-century French philosopher William of Soissons, demand us to accept that anything, including

its own negation, can be proven or can be inferred from a contradiction. Respecting the principle of explosion, the existence of a contradiction (or the existence of logical inconsistency) in a scientific theorem, rule et cetera is disastrous. However, the historical development of science shows that scientist inevitably revise the theories, false positions and claims are identified once and again, and we all make different kind of mistakes. In order to avert a disproportionately great damage on science and to prevent reducing science into pure subjective belief, a negation of the principle of explosion is required. Nonetheless, a justified negation of **the ex contradictione quodlibet principle** (Carnielli and Marcos, 2001) does not imply the correctness of paraconsistent logic (Carnielli and Marcos, 2001, da Costa, 1974, 1958, Priest, 1998, Priest et al., 1989, Quesada, 1977) as such as advocated especially by the Peruvian philosopher Francisco Miró Quesada (Quesada, 1977) and other (Carnielli and Marcos, 2001, da Costa, 1974, 1958, Priest, 1998, Priest et al., 1989). In general, scientific theories appear to progress from lower and simpler to higher and more complex levels. However, high level theories cannot be taken for granted because high level theories are grounded on a lot of assumptions, definitions and other procedures and may rest upon too much erroneous stuff even if still not identified. Therefore, it should be considered to check at lower at simpler levels like with like.

2.6.3. Axiom III. Lex negationis

$$\neg(0) \times 0 = 1 \tag{142}$$

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, 1990b). In this context, there is some evidence that $\neg(1) \times 1 = 0$. In other words, it is $(\neg(1) \times 1) \times (\neg(0) \times 0) = 1$. Concepts like identity, difference, negation, opposition et cetera engaged the attention of scholars at least over the last twenty-three centuries (see also Horn, 1989, Speranza and Horn, 2010). As long as we first and foremost follow Josiah Royce, negatio or negation "is one of the simplest and most fundamental relations known to the human mind. For the study of logic, no more important and fruitful relation is known." (see also Royce, 1917, p. 265) But, do we really know what, for sure, what negation is? Based on what we know about negation, Aristotle (see also Wedin, 1990a) has been one of the first to present a theory of negation, which can be found in discontinuous chunks in his works the Metaphysics, the Categories, De Interpretatione, and the Prior Analytics (see also Horn, 1989, p. 1). Negation (see also Newstadt, 2015) as a fundamental philosophical concept found its own very special melting point especially in Hegel's dialectic and is more than just a formal logical process or operation which converts only true to false and false to true. Negation as such is a natural process too and equally '**an engine of changes of objective reality** " (see also Barukčić, 2019a). However, it remains an open question to establish a generally accepted link between this fundamental philosophical concept and an adequate counterpart in physics, mathematics and mathematical statistics et cetera. Especially the relationship between creatio ex nihilio (see also Donnelly, 1970, Ehrhardt, 1950, Ford, 1983) determination and negation (see also Ayer, 1952, Hedwig, 1980, Heinemann, Fritz H., 1943, Kunen, 1987) has been discussed in science since ancient (see also Horn, 1989, Speranza and Horn, 2010) times too. The development of the notion of negation leads from Aristotle to Meister Eckhart von Hochheim, commonly known as

Meister Eckhart (see also Tsopurashvili, 2012) or Eckehart, to Spinoza (1632 – 1677), to Immanuel Kant (1724-1804) and finally to Georg Wilhelm Friedrich Hegel (1770-1831) and other authors too. One point is worth being noted, even if it does not come as a surprise, it was especially Benedict de Spinoza (1632 – 1677) as one of the philosophical founding fathers of the Age of Enlightenment who addressed the relationship between determination and negation in his lost letter of June 2, 1674 to his friend Jarig Jelles (see also Förster and Melamed, 2012) by the discovery of his fundamental insight that " **determinatio negatio est**" (see also Spinoza, 1674, p. 634). Hegel went even so far as to extended the slogan raised by Spinoza into to "Omnis determinatio est negatio" (see also Hegel, Georg Wilhelm Friedrich, 1812b, 2010, p. 87). Finally, it did not take too long, and the notion of negation entered the world of mathematics and mathematical logic at least with Boole's (see also Boole, 1854) publication in the year 1854. "Let us, for simplicity of conception, give to the symbol x the particular interpretation of men, then 1 - x will represent the class of 'not-men'." (see also Boole, 1854, p. 49). The notion of negation found his way to physics by the contribution of authors like Woldemar Voigt (Voigt (1850-1919), 1887), George Francis FitzGerald (FitzGerald (1851-1901), 1889), Hendrik Antoon Lorentz (Lorentz (1853-1928), 1892), Joseph Larmor (Larmor (1857-1942), 1897), Jules Henri Poincaré (Poincaré (1854-1912), 1905) and Albert Einstein (1879-1955) (A. Einstein, 1905b) on the notion "Lorentz factor".

3. Results

3.1. HPV vaccination and cervical cancer I

Some aspects of the data and the statistical analysis of the study of Lei et al. [18] are presented by table 1. The index of independence is about p(IOI)= 0,315193878 and indicates, that the data presented are of use to some extent in order to be analysed for an exclusion relationship and causal relationships. The causal relationship is negative and significant (k = -0,0110511076; p Value left tailed (HGD) = 0,0000000). The data are not self-contradictory. The exclusion relationship p(EXCL) with p(EXCL)= 0,9999886430 (P Value = 0,0000113569) is highly significant. Nonetheless, the exclusion relationship is at least p (EXCL) approx.= 0,9658886894. In other words, an HPV vaccination excludes human cervical cancer (P Value = 0,0000113569) and protects against human cervical cancer.

3.2. HPV vaccination and cervical cancer II

Other aspects of the data and the statistical analysis of the study of Lei et al. [19] are presented by table 2. The index of independence is about p(IOI)= 0,315193878 and indicates, that the data presented are of use to some extent in order to be analysed for an exclusion relationship and causal relationships. The causal relationship is negative and significant (k = -0,0107351051; p Value left tailed (HGD) =

[18]Lei J, Ploner A, Elfström KM, Wang J, Roth A, Fang F, Sundström K, Dillner J, Sparén P. HPV Vaccination and the Risk of Invasive Cervical Cancer. N Engl J Med. 2020 Oct 1;383(14):1340-1348. doi: 10.1056/NEJMoa1917338. PMID: 32997908.

[19]Lei J, Ploner A, Elfström KM, Wang J, Roth A, Fang F, Sundström K, Dillner J, Sparén P. HPV Vaccination and the Risk of Invasive Cervical Cancer. N Engl J Med. 2020 Oct 1;383(14):1340-1348. doi: 10.1056/NEJMoa1917338. PMID: 32997908.

0,0000000). The data are not self-contradictory. The exclusion relationship p(EXCL) with p(EXCL)= 0,9999988045 (P Value = 0,0000011955) is highly significant. Nonetheless, the exclusion relationship is at least p (EXCL) approx.= 0,9964093357. In other words, an HPV vaccination excludes human cervical cancer (P Value = 0,0000011955)and protects against human cervical cancer. However, 2 out of, 1672983 participants were not protected against human cervical cancer by HPV vaccine. Two girls before the age of 17 years were vaccinated against HPV, but suffered from human cervical cancer. The question is, were these two girls already infected with HPV somehow (i.e. early sexual activity) before they were vaccinated against HPV, and what are the consequences?

4. Discussion

The human papilloma virus has a very long history. Firstly, it was possible to demonstrate the infectivity of human warts over 100 years ago [20] . Secondly, the causal agent, a human papillomavirus (HPV), was displayed with the electron microscope in 1949 [21] , [22] , [23] . However, it was Crawford [24] who examined the DNA of human papilloma virus by a variety of physical techniques in the year 1965. It lasted not for a long time and the relationship between HPV and cervical cancer has been discussed [25] too. Especially Harald zur Hausen, who studied viruses at the German Cancer Research Center in Heidelberg, Germany, discovered that certain strains of the human papilloma virus are "key contributors to cervical cancer."[26] , [27] As science developed, Zur Hausen's tendency became apparent to add an own 'causality criterion'to the classical *Henle(Henle, 1840) (1809–1885) - Koch(Koch, 1878) (1843–1910) postulates* (Carter, 1985): a special viral genome should be transcriptionally active and persistently present in the cancer. The crux of the matter is that zur Hausen provided evidence that HPV viruses are "$\cdots$ key contributors to cervical cancer"[28] but not that HPV is the cause or a cause of human cervical cancer. A point which is necessary to monitor very carefully it that for the first time in history, it was Barukčić [29] who provided in the year 2018 convincing evidence that HPV is the cause of human cervical cancer (see also Barukčić, 2018b). The study of Lei et al. [30] with a sample size of N = 1672983 participants confirmed the Barukčić's methods and Barukčić's (see also Barukčić, 2018b) findings from 2018 in a way never seen before.

5. Conclusion

It is confirmed that human papilloma virus is the cause of human cervical cancer (P Value = 0,0000011955) as already established 2018 by Barukčić (see also Barukčić, 2018b).

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6. Patient consent for publication

Not required.

Conflict of interest statement

No conflict of interest to declare.

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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