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Without Epstein–Barr virus infection, no nasopharyngeal carcinoma

Research article

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Abstract

Background:

The relationship between an Epstein-Barr virus infection and nasopharyngeal carcinoma has been re-investigated.

Methods:

The data as published by the study of Jingtao Cui et al. were re-analysed and tested for a necessary condition relationship between an Epstein-Barr virus infection and nasopharyngeal carcinoma.

Results:

The necessary condition relationship between an Epstein-Barr virus infection and nasopharyngeal carcinoma is equal to +1 and highly significant.

Conclusion:

Without an Epstein-Barr virus infection, no nasopharyngeal carcinoma.

Keywords: Epstein-Barr virus; Nasopharyngeal carcinoma; Conditio sine qua non; Cause; Effect; Causation

1. Introduction

Nasopharyngeal carcinoma (NPC), originating from the fossa of Rosenmüller of the nasopharynx, is rare [1] epithelial malignancy in most of the human populations worldwide. Nonetheless, in southern [2] China, the incidence rate of NPC is about 20 to 40 cases per 100,000 individuals per year. Several risk factors including diet[3] , [4] lifestyle (smoking, alcohol consumption et cetera) [5] and viral infections

[1] Yu MC, Yuan JM. Epidemiology of nasopharyngeal carcinoma. Semin Cancer Biol. 2002 Dec;12(6):421-9. doi: 10.1016/s1044579x02000858. PMID: 12450728.

[2] Zhang LF, Li YH, Xie SH, Ling W, Chen SH, Liu Q, Huang QH, Cao SM. Incidence trend of nasopharyngeal carcinoma from 1987 to 2011 in Sihui County, Guangdong Province, South China: an age-period-cohort analysis. Chin J Cancer. 2015 May 14;34(8):350-7. doi: 10.1186/s40880-015-0018-6. PMID: 26058679; PMCID: PMC4593377.

[3] Zheng YM, Tuppin P, Hubert A, Jeannel D, Pan YJ, Zeng Y, de Thé G. Environmental and dietary risk factors for nasopharyngeal carcinoma: a case-control study in Zangwu County, Guangxi, China. Br J Cancer. 1994 Mar;69(3):508-14. doi: 10.1038/bjc.1994.92. PMID: 8123482; PMCID: PMC1968852.

[4] Yu MC. Nasopharyngeal carcinoma: epidemiology and dietary factors. IARC Sci Publ. 1991;(105):39-47. PMID: 1855886.

[5] Jia WH, Qin HD. Non-viral environmental risk factors for nasopharyngeal carcinoma: a systematic review. Semin Cancer Biol. 2012 Apr;22(2):117-26. doi: 10.1016/j.semcancer.2012.01.009. Epub 2012 Jan 30. PMID: 22311401.

[6] [7] , occupational exposure to dust, consumption of salted fish, and genetic factors et cetera have been claimed to contribute to the development of NPC. However, results across various studies with respect to risk factors have not been entirely consistent. More and more, Epstein-Barr [8] , [9] virus (EBV), discovered in 1964 and known as human herpes virus type 4 (HHV4), has been linked to NPC, first discovered by high titres of serum antibodies against EBV antigens detected in NPC patients[10]. It is well known that more than 95% of all people [11] become infected with EBV at some point in time in their life while the majority of infections appears to occur in children and teenagers. [12] Besides of the still unknown and complex aetiology of nasopharyngeal carcinoma [13] the relationship between EBV and NPC is becoming more and more urgent.

2. Material and methods

Scientific knowledge and objective reality are more than interrelated. 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

2.1.1. Statistical methods

The probability of the necessary (Barukčić, 2021c) condition p(SINE) has been calculated and tested for statistical significance. The probability of the sufficient (Barukčić, 2021c) condition p(IMP) has been calculated, the statistical significance of this relationship has been proofed. The chi-square

[6]Gunvén P, Klein G, Henle G, Henle W, Clifford P. Epstein-Barr virus in Burkitt's lymphoma and nasopharyngeal carcinoma. Antibodies to EBV associated membrane and viral capsid antigens in Burkitt lymphoma patients. Nature. 1970 Dec 12;228(5276):1053-6. doi: 10.1038/2281053a0. PMID: 4320656.

[7]Tsao SW, Tsang CM, Lo KW. Epstein-Barr virus infection and nasopharyngeal carcinoma. Philos Trans R Soc Lond B Biol Sci. 2017 Oct 19;372(1732):20160270. doi: 10.1098/rstb.2016.0270. PMID: 28893937; PMCID: PMC5597737.

[8]EPSTEIN MA, ACHONG BG, BARR YM. VIRUS PARTICLES IN CULTURED LYMPHOBLASTS FROM BURKITT'S LYMPHOMA. Lancet. 1964 Mar 28;1(7335):702-3. doi: 10.1016/s0140-6736(64)91524-7. PMID: 14107961.

[9]Epstein A. Why and How Epstein-Barr Virus Was Discovered 50 Years Ago. Curr Top Microbiol Immunol. 2015;390(Pt 1):3-15. doi: 10.1007/978-3-319-22822-8_1. PMID: 26424640.

[10]Gunvén P, Klein G, Henle G, Henle W, Clifford P. Epstein-Barr virus in Burkitt's lymphoma and nasopharyngeal carcinoma. Antibodies to EBV associated membrane and viral capsid antigens in Burkitt lymphoma patients. Nature. 1970 Dec 12;228(5276):1053-6. doi: 10.1038/2281053a0. PMID: 4320656.

[11]Cui J, Yan W, Xu S, Wang Q, Zhang W, Liu W, Ni A. Anti-Epstein-Barr virus antibodies in Beijing during 2013-2017: What we have found in the different patients. PLoS One. 2018 Mar 1;13(3):e0193171. doi: 10.1371/journal.pone.0193171. PMID: 29494658; PMCID: PMC5832223.

[12]Cohen JI. Epstein-Barr virus infection. N Engl J Med. 2000 Aug 17;343(7):481-92. doi: 10.1056/NEJM200008173430707. PMID: 10944566.

[13]Chang ET, Adami HO. The enigmatic epidemiology of nasopharyngeal carcinoma. Cancer Epidemiol Biomarkers Prev. 2006 Oct;15(10):1765-77. doi: 10.1158/1055-9965.EPI-06-0353. PMID: 17035381.

goodness of fit test with one degree of freedom has been used to test whether the sample data published fit a certain theoretical distribution in the population. The causal relationship k (Barukčić, 2021c) has been calculated to evaluate a possible causal relationship between the events/factors analysed. The hyper-geometric(Fisher, 1922, Gonin, 1936, Huygens and van Schooten, 1657, Pearson, 1899) distribution (HGD) has been used to test the one-sided significance of the causal relationship k. Potential publication bias among the studies included is assessed by Begg's funnel plot [14] , [15] , [16] , [17] with a treatment effect (horizontal axis) and some measure of weight (inverse variance, standard error, sample size et cetera) on the vertical axis . 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 [18] , [19] , [20] . Under usual circumstances, an I^2 value of 25%, 50% and 75% are regarded as low, moderate and high heterogeneity[21]. In this publication, the study (design) bias and the heterogeneity among the studies has been controlled by IOI, the index of independence(Barukčić, 2019a) and IOU, the index of unfairness(Barukčić, 2019b). All the data were analysed using Microsoft Excel® version 14.0.7166.5000 (32 - Bit) software (Microsoft Corporation, USA). The p values less than 0.05 were considered to indicate a statistically significant difference.

2.1.2. Study design and bias

Systematic observation and experimentation, inductive and deductive reasoning are essential for any formation and testing of hypotheses and theories about the natural world. In one way or another, logically and mathematically sound scientific methods and concepts are crucial constituents of any scientific progress. When all goes well, different scientists at different times and places using the same scientific methodology should be able to generate the same scientific knowledge. However, more than half (52%) of scientists surveyed believe that studies do not successfully reproduce sufficiently similar or the same results as the original studies (Baker, 2016). In a very large study on publication bias in meta-analyses, Kicinski et al. (Kicinski et al., 2015) found evidence of publication bias even in systematic reviews. Therefore, a careful re-evaluation of the study/experimental design, the statistical methods and other scientific means which underpin scientific inquiry and research goals appears to be necessary once and again. While it is important to 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

[14] Light RJ, Pillemer DB. Summing up. The science of reviewing research. Cambridge, MA: Harvard University Press, 1984.

[15] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997 Sep 13;315(7109):629-34. doi: 10.1136/bmj.315.7109.629. PMID: 9310563; PMCID: PMC2127453.

[16] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994 Dec;50(4):1088-101. PMID: 7786990.

[17] Lau J, Ioannidis JP, Terrin N, Schmid CH, Olkin I. The case of the misleading funnel plot. BMJ. 2006 Sep 16;333(7568):597-600. doi: 10.1136/bmj.333.7568.597. PMID: 16974018; PMCID: PMC1570006.

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

[19] 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.

[20] 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.

[21] 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.

provide information about the credibility of the data.

Index of unfairness (IOU)

Definition 2.1 (**Index of unfairness**)**.**

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

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

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

Index of independence (IOI)

Definition 2.2 (**Index of independence**)**.**

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

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

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

2.2. 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 need to be logically consistent and correct.

2.2.1. 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.

2.2.2. 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. 10) becomes

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

but not general. The "local hidden variable "$E(\underline{X})$ follows as $E(\underline{X}) \equiv \frac{\sigma(X)^2}{E(X)}$.

In our understanding, there are circumstances where the relationship between geometry or Pythagorean theorem, Euclid's theorem and probability theory / statistics is given by the equation (see figure 1)

$$a^2 \equiv E\left(X^2\right) \tag{5}$$

Further research should be able and might provide convincing evidence whether - and to what extent - equation 5 makes any sense.

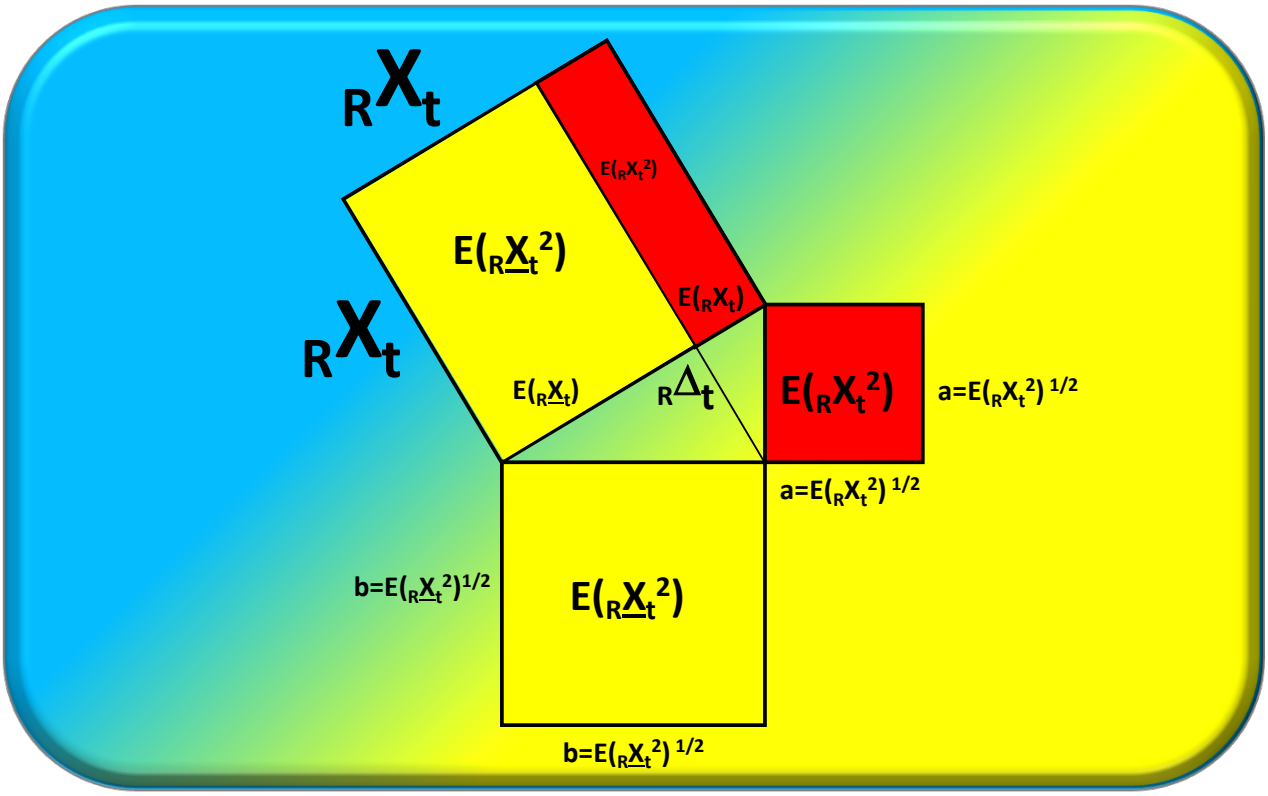

Figure 1. Geometry and probability theory.

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

$$\begin{aligned} E(X)^2 &\equiv p(X) \times X \times p(X) \times X \\ &\equiv p(X) \times p(X) \times X \times X \\ &\equiv (p(X) \times X)^2 \\ &\equiv E(X) \times E(X) \end{aligned} \tag{6}$$

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:

$$E\left(X_{kl\mu\nu\dots}\right) \equiv p\left(X_{kl\mu\nu\dots}\right) \times X_{kl\mu\nu\dots} \equiv p\left(X_{kl\mu\nu\dots}\right) \cap X_{kl\mu\nu\dots} \tag{7}$$

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

$$\begin{aligned} {}^{2}E\left(X_{\mathrm{kl}\mu\nu\ldots}\right) &\equiv p\left(X_{\mathrm{kl}\mu\nu\ldots}\right)\times X_{\mathrm{kl}\mu\nu\ldots}\times p\left(X_{\mathrm{kl}\mu\nu\ldots}\right)\times X_{\mathrm{kl}\mu\nu\ldots} \\ &\equiv p\left(X_{\mathrm{kl}\mu\nu\ldots}\right)\times p\left(X_{\mathrm{kl}\mu\nu\ldots}\right)\times X_{\mathrm{kl}\mu\nu\ldots}\times X_{\mathrm{kl}\mu\nu\ldots} \\ &\equiv {}^{2}\left(p\left(X_{\mathrm{kl}\mu\nu\ldots}\right)\times X_{\mathrm{kl}\mu\nu\ldots}\right) \\ &\equiv E\left(X_{\mathrm{kl}\mu\nu\ldots}\right)\times E\left(X_{\mathrm{kl}\mu\nu\ldots}\right) \end{aligned} \tag{8}$$

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:*

$$\begin{aligned} E\left(X^{2}\right) &\equiv p\left(X\right)\times X^{2} \\ &\equiv \left(p\left(X\right)\times X\right)\times X \\ &\equiv E\left(X\right)\times X \\ &\equiv X\times E\left(X\right) \end{aligned} \tag{9}$$

From the point of view of tensor algebra it is

$$\begin{aligned} E\left({}^{2}X_{\mathrm{kl}\mu\nu\ldots}\right) &\equiv p\left(X_{\mathrm{kl}\mu\nu\ldots}\right)\times {}^{2}X_{\mathrm{kl}\mu\nu\ldots} \\ &\equiv \left(p\left(X_{\mathrm{kl}\mu\nu\ldots}\right)\times X_{\mathrm{kl}\mu\nu\ldots}\right)\times X_{\mathrm{kl}\mu\nu\ldots} \\ &\equiv E\left(X_{\mathrm{kl}\mu\nu\ldots}\right)\times X_{\mathrm{kl}\mu\nu\ldots} \\ &\equiv X_{\mathrm{kl}\mu\nu\ldots}\times E\left(X_{\mathrm{kl}\mu\nu\ldots}\right) \end{aligned} \tag{10}$$

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:*

$$\begin{aligned} E\left(X^{n}\right) &\equiv p\left(X\right)\times X^{n} \\ &\equiv \left(p\left(X\right)\times X\right)\times X^{n\text{-}1} \\ &\equiv E\left(X\right)\times X^{n\text{-}1} \end{aligned} \tag{11}$$

2.2.3. Probability of a Random Variable

The probability p(X) of a random variable X follows as (see equation 3)

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

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

2.2.4. 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 9):

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

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 [22] 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, 1812, 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).

[22] 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*

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

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 too 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

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

2.2.5. Bernoulli distribution

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

Definition 2.11 (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 1 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 1. The two by two table of Bernoulli random variables

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

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 '.

2.2.6. Binomial random variables

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

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

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, Ilija, 2022) as

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

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

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

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

2.2.7. Independence

Definition 2.14 (Independence).

The philosophical, mathematical(Kolmogoroff, Andreĭ Nikolaevich, 1933) and physical(Einstein, 1948) concept of independence is of fundamental(Kolmogoroff, Andreĭ Nikolaevich, 1933) importance in (natural) sciences as such. In fact, it is insightful to recall again before the mind's eye Einstein's theoretical approach to the concept of independence. "*Ohne die Annahme einer ... Unabhängigkeit der ... Dinge voneinander ... wäre physikalisches Denken ... nicht möglich.*"(Einstein, 1948).

In general, an event A_t at the Bernoulli trial t need not but can be independent of the existence or of the occurrence of another event B_t *at the same* Bernoulli trial t. Mathematically(Moivre, 1718), independence (Kolmogoroff, Andreĭ Nikolaevich, 1933) in terms of probability theory is defined at the same (period of) time (i.e. Bernoulli trial) t as

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

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

$$p\left(b_{\mathrm{t}}\right) \equiv p\left(A_{\mathrm{t}}\right) \times p\left(\underline{B}_{\mathrm{t}}\right) \tag{66}$$

or

$$p\left(c_{\mathrm{t}}\right) \equiv p\left(\underline{A}_{\mathrm{t}}\right) \times p\left(B_{\mathrm{t}}\right) \tag{67}$$

and

$$p\left(d_{\mathrm{t}}\right) \equiv p\left(\underline{A}_{\mathrm{t}}\right) \times p\left(\underline{B}_{\mathrm{t}}\right) \tag{68}$$

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 $\mathrm{A_t}$ (condition) enables or guarantees the presence of another event $\mathrm{B_t}$ (conditioned). As a result of these thoughts, another question worth asking concerns the relationship between the independence of an event $\mathrm{A_t}$ (a condition) and another event $\mathrm{B_t}$ (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 $\mathrm{A_t}$ (a condition) is a necessary condition of event $\mathrm{B_t}$ (conditioned) even under circumstances where the event $\mathrm{A_t}$ (a condition) (a necessary condition) is independent of an event $\mathrm{B_t}$ (conditioned)? This question is already answered more or less to the negative (Barukčić, 2018b). An event $\mathrm{A_t}$ which is a necessary condition of another event $\mathrm{B_t}$ is equally an event without which another event ($\mathrm{B_t}$) could not be, could not occur, and implies as such already a kind of dependence. However, it is not mandatory that such a kind of dependence is a causal one. Thus far, **data which provide evidence of a significant conditio sine qua non relationship between two events like $\mathbf{A_t}$ and $\mathbf{B_t}$ and equally support the hypothesis that $\mathbf{A_t}$ and $\mathbf{B_t}$ 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.

2.2.8. Dependence

Definition 2.15 (**Dependence**)**.**

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

$$p\left(\underbrace{A_{\mathrm{t}} \wedge B_{\mathrm{t}} \wedge C_{\mathrm{t}} \wedge \ldots}_{n \text{ random variables}}\right) \equiv \sqrt[n]{\underbrace{p\left(A_{\mathrm{t}}\right) \times p\left(B_{\mathrm{t}}\right) \times p\left(C_{\mathrm{t}}\right) \times \ldots}_{n \text{ random variables}}} \tag{69}$$

2.2.9. Odds ratio (OR)

Definition 2.16 (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 3. The odds' ratio (OR) is defined as

Table 3. The two by two table of random variables

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

$$\begin{aligned} OR(A_t, B_t) &\equiv \left(\frac{a_t}{b_t}\right) / \left(\frac{c_t}{d_t}\right) \\ &\equiv \left(\frac{a_t \times d_t}{b_t \times c_t}\right) \end{aligned} \tag{70}$$

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. 70. 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. 70. 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.

2.2.10. Relative risk (RR)

Relative risk (RR_{nc})

Definition 2.17 (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

$$\begin{aligned} RR(A_t, B_t)_{nc} &\equiv \frac{\frac{p(a_t)}{p(A_t)}}{\frac{p(c_t)}{p(NotA_t)}} \\ &\equiv \frac{p(a_t) \times p(NotA_t)}{p(c_t) \times p(A_t)} \\ &\equiv \frac{N \times p(a_t) \times N \times p(NotA_t)}{N \times p(c_t) \times N \times p(A_t)} \\ &\equiv \frac{a_t \times (NotA_t)}{c_t \times A_t} \\ &\equiv \frac{EER\,(A_t, B_t)}{CER\,(A_t, B_t)} \end{aligned} \tag{71}$$

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.

Relative risk (RR (sc))

Definition 2.18 (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

$$\begin{aligned} RR(A_t, B_t)_{sc} &\equiv \frac{\frac{p(a_t)}{p(B_t)}}{\frac{p(b_t)}{p(NotB_t)}} \\ &\equiv \frac{p(a_t) \times p(NotB_t)}{p(b_t) \times p(B_t)} \\ &\equiv \frac{N \times p(a_t) \times N \times p(NotB_t)}{N \times p(b_t) \times N \times p(B_t)} \\ &\equiv \frac{a_t \times (NotB_t)}{b_t \times B_t} \\ &\equiv \frac{OPR\,(A_t, B_t)}{CPR\,(A_t, B_t)} \end{aligned} \tag{72}$$

Relative risk reduction (RRR)

Definition 2.19 (Relative risk reduction (RRR))**.**

$$\begin{aligned} RRR\,(A_t, B_t) &\equiv \frac{CER\,(A_t, B_t) - EER\,(A_t, B_t)}{CER\,(A_t, B_t)} \\ &= 1 - RR(A_t, B_t) \end{aligned} \tag{73}$$

Vaccine efficacy (VE)

Definition 2.20 (Vaccine efficacy (VE))**.**

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

$$\begin{aligned} VE\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) &\equiv 100 \times \left(1 - RR\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right)\right) \\ &\equiv 100 \times \left(\frac{CER\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) - EER\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right)}{CER\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right)}\right) \end{aligned} \tag{74}$$

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

Experimental event rate (EER)

Definition 2.21 (Experimental event rate (EER))**.**

$$EER\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) \equiv \frac{p(a_{\mathrm{t}})}{p(A_{\mathrm{t}})} = \frac{a_{\mathrm{t}}}{a_{\mathrm{t}} + b_{\mathrm{t}}} \tag{75}$$

Definition 2.22 (Control event rate (CER))**.**

$$CER\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) \equiv \frac{p(c_{\mathrm{t}})}{p(\underline{A}_{\mathrm{t}})} = \frac{c_{\mathrm{t}}}{c_{\mathrm{t}} + d_{\mathrm{t}}} \tag{76}$$

Absolute risk reduction (ARR)

Definition 2.23 (Absolute risk reducation (ARR))**.**

$$\begin{aligned} ARR\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) &\equiv \frac{p(c_{\mathrm{t}})}{p(\underline{A}_{\mathrm{t}})} - \frac{p(a_{\mathrm{t}})}{p(A_{\mathrm{t}})} \\ &= \frac{c_{\mathrm{t}}}{c_{\mathrm{t}} + d_{\mathrm{t}}} - \frac{a_{\mathrm{t}}}{a_{\mathrm{t}} + b_{\mathrm{t}}} \\ &= CER\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) - EER\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) \end{aligned} \tag{77}$$

Absolute risk increase (ARI)

Definition 2.24 (Absolute risk increase (ARI))**.**

$$\begin{aligned} ARI\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) &\equiv \frac{p\left(a_{\mathrm{t}}\right)}{p\left(A_{\mathrm{t}}\right)} - \frac{p\left(c_{\mathrm{t}}\right)}{p\left(\underline{A}_{\mathrm{t}}\right)} \\ &= EER\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) - CER\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) \end{aligned} \tag{78}$$

Number needed to treat (NNT)

Definition 2.25 (Number needed to treat (NNT))**.**

$$NNT\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) \equiv \frac{1}{CER\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) - EER\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right)} \tag{79}$$

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

Number needed to harm (NNH)

Definition 2.26 (Number needed to harm (NNH))**.**

$$NNH\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) \equiv \frac{1}{EER\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) - CER\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right)} \tag{80}$$

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

Outcome prevalence rate (OPR)

Definition 2.27 (Outcome prevalence rate (OPR))**.**

$$OPR\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right) \equiv \frac{p\left(a_{\mathrm{t}}\right)}{p\left(B_{\mathrm{t}}\right)} = \frac{a_{\mathrm{t}}}{a_{\mathrm{t}} + c_{\mathrm{t}}} \tag{81}$$

Control prevalence rate (CPR)

Definition 2.28 (Control prevalence rate (CPR))**.**

$$CPR\,(A_{\mathrm{t}},B_{\mathrm{t}}) \equiv \frac{p(b_{\mathrm{t}})}{p(\underline{B}_{\mathrm{t}})} = \frac{b_{\mathrm{t}}}{b_{\mathrm{t}}+d_{\mathrm{t}}} \tag{82}$$

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

Absolute prevalence reduction (APR)

Definition 2.29 (Absolute prevalence reduction (APR))**.**

$$APR\,(A_{\mathrm{t}},B_{\mathrm{t}}) \equiv CPR\,(A_{\mathrm{t}},B_{\mathrm{t}}) - OPR\,(A_{\mathrm{t}},B_{\mathrm{t}}) \tag{83}$$

Absolute prevalence increase (API)

Definition 2.30 (Absolute prevalence increase (API))**.**

$$API\,(A_{\mathrm{t}},B_{\mathrm{t}}) \equiv OPR\,(A_{\mathrm{t}},B_{\mathrm{t}}) - CPR\,(A_{\mathrm{t}},B_{\mathrm{t}}) \tag{84}$$

Relative prevalence reduction (RPR)

Definition 2.31 (Relative prevalence reduction (RPR))**.**

$$\begin{aligned} RPR\,(A_{\mathrm{t}},B_{\mathrm{t}}) &\equiv \frac{CPR\,(A_{\mathrm{t}},B_{\mathrm{t}}) - OPR\,(A_{\mathrm{t}},B_{\mathrm{t}})}{CPR\,(A_{\mathrm{t}},B_{\mathrm{t}})} \\ &= 1 - RR(A_{\mathrm{t}},B_{\mathrm{t}})_{\mathrm{sc}} \end{aligned} \tag{85}$$

The index NNS

Definition 2.32 (The index NNS)**.**

$$NNS\left(A_t, B_t\right) \equiv \frac{1}{CPR\left(A_t, B_t\right) - OPR\left(A_t, B_t\right)} \tag{86}$$

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

The index NNI

Definition 2.33 (The index NNI)**.**

$$NNI\left(A_t, B_t\right) \equiv \frac{1}{OPR\left(A_t, B_t\right) - CPR\left(A_t, B_t\right)} \tag{87}$$

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

2.2.11. Index of relationship (IOR)

Definition 2.34 (Index of relationship (IOR))**.**

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

$$\begin{aligned} IOR(A_t, B_t) &\equiv \left(\frac{p(A_t \wedge B_t)}{p(B_t) \times p(A_t)}\right) - 1 \\ &\equiv \left(\frac{p(a_t)}{p(B_t) \times p(A_t)}\right) - 1 \\ &\equiv \left(\left(\frac{N \times N \times p(a_t)}{N \times p(B_t) \times N \times p(A_t)}\right) - 1\right) \\ &\equiv \left(\left(\frac{N \times a}{A \times B}\right) - 1\right) \end{aligned} \tag{88}$$

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

2.3. Conditions

2.3.1. Exclusion relationship

Definition 2.35 (**Exclusion relationship [*EXCL*]**).

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

$$\begin{aligned} p(A_t \mid B_t) &\equiv p(A_t \uparrow B_t) \\ &\equiv p(b_t) + p(c_t) + p(d_t) \\ &\equiv \frac{N \times (p(b_t) + p(c_t) + p(d_t))}{N} \\ &\equiv \frac{\sum_{t=1}^{N} (\underline{A}_t \vee \underline{B}_t)}{N} \equiv \frac{b+c+d}{N} \\ &\equiv \frac{b+\underline{A}}{N} \\ &\equiv \frac{c+\underline{B}}{N} \\ &\equiv +1 \end{aligned} \tag{89}$$

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

Table 4. A_t excludes B_t and vice versa.

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

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

$$\begin{aligned} p(Vaccine : BNT162b2 \mid COVID-19(infection)) &\equiv p(b_t) + p(c_t) + p(d_t) \\ &\equiv 1 - p(a_t) \\ &\equiv 1 - \left(\frac{8}{43538}\right) \\ &\equiv +0,99981625 \end{aligned} \tag{90}$$

with a P Value = 0,000184.

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

$$\begin{aligned} p\left(A_t \mid B_t\right) &\equiv p\left(\underline{A}_t \cup \underline{B}_t\right) \\ &\equiv 1 - p\left(A_t \cap B_t\right) \\ &\equiv 1 - \int_{-\infty}^{A_t} \int_{-\infty}^{B_t} f\left(A_t, B_t\right)\, dA_t\, dB_t \\ &\equiv +1 \end{aligned} \tag{91}$$

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

2.3.2. Observational study and exclusion relationship

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

$$p\left(A_t \mid B_t\right) \equiv p\left(A_t \uparrow B_t\right) \geq 1 - \frac{p\left(a_t\right)}{p\left(B_t\right)} \tag{92}$$

2.3.3. Experimental study and exclusion relationship

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

$$p\left(A_t \mid B_t\right) \equiv p\left(A_t \uparrow B_t\right) \geq 1 - \frac{p\left(a_t\right)}{p\left(A_t\right)} \tag{93}$$

2.3.4. The goodness of fit test of an exclusion relationship

Definition 2.36 (The $\tilde{\chi}^2$ goodness of fit test of an exclusion relationship).

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

$$\begin{aligned}\tilde{\chi}^2{}_{\text{Calculated}}\left((A_{\text{t}} \mid B_{\text{t}}) \mid A\right) &\equiv \frac{(b-(a+b))^2}{A}+ \\ &\quad \frac{((c+d)-\underline{A})^2}{\underline{A}} \\ &\equiv \frac{a^2}{A}+0 \\ &\equiv \frac{a^2}{A}\end{aligned} \tag{94}$$

or equally as

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

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

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

Definition 2.37 (**The left-tailed p Value of an exclusion relationship**).

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

$$\begin{aligned}pValue_{\text{lt}}\left(A_{\text{t}} \mid B_{\text{t}}\right) &\equiv 1-e^{-(1-p(A_{\text{t}}|B_{\text{t}}))} \\ &\equiv 1-e^{-(a/N)}\end{aligned} \tag{96}$$

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

2.3.6. Neither nor conditions

Definition 2.38 (**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

$$\begin{aligned} p\left(A_t \downarrow B_t\right) &\equiv p\left(d_t\right) \\ &\equiv \frac{N - \sum_{t=1}^{N} \left(A_t \vee B_t\right)}{N} \equiv \frac{\sum_{t=1}^{N} \left(\underline{A}_t \wedge \underline{B}_t\right)}{N} \equiv \frac{N \times \left(p\left(d_t\right)\right)}{N} \\ &\equiv \frac{d}{N} \\ &\equiv +1 \end{aligned} \tag{97}$$

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

Definition 2.39 (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

$$\begin{aligned} {\tilde{\chi}^2}_{\text{Calculated}}\left(\left(A_t \downarrow B_t\right) \mid A\right) &\equiv \frac{\left(d - \left(c + d\right)\right)^2}{\underline{A}} + \\ &\quad \frac{\left(\left(a + b\right) - A\right)^2}{A} \\ &\equiv \frac{c^2}{\underline{A}} + 0 \end{aligned} \tag{98}$$

or equally as

$$\begin{aligned} {\tilde{\chi}^2}_{\text{Calculated}}\left(\left(A_t \downarrow B_t\right) \mid B\right) &\equiv \frac{\left(d - \left(b + d\right)\right)^2}{\underline{B}} + \\ &\quad \frac{\left(\left(a + c\right) - B\right)^2}{B} \\ &\equiv \frac{b^2}{\underline{B}} + 0 \end{aligned} \tag{99}$$

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

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

Definition 2.40 (The left-tailed p Value of a neither A_t nor B_t condition relationship).

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

$$\begin{aligned} pValue_{\text{lt}}\left(A_t \downarrow B_t\right) &\equiv 1 - e^{-(1-p(A_t \downarrow B_t))} \\ &\equiv 1 - e^{-p(A_t \vee B_t)} \\ &\equiv 1 - e^{-((a+b+c)/N)} \end{aligned} \tag{100}$$

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

Table 5. Neither A_t nor B_t relationship.

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

2.3.9. Necessary condition

Definition 2.41 (**Necessary condition [*Conditio sine qua non*]**).

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

> "... everything which has a ... ... potency in question ... ... has the potency ... of acting ... not in all circumstances but on certain conditions ... "

(see also Aristotle et al., 1908, Metaphysica IX 5 1048a 14-19)

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

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

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

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

In point of fact, Aristotle developed a theory of conditions and causality commonly referred to as the doctrine of four causes. Many aspects and general features of Aristotle's logical concept of causality are meanwhile extensively and critically debated in secondary literature. However, even if the Greek philosophers Heraclitus, Plato, Aristotle et cetera numbers among the greatest philosophers of all time, the philosophy has evolved. Scientific knowledge and objective reality are deeply interrelated and cannot be reduced only to Greek philosophers like Aristotle. 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

$$\begin{aligned} p\left(A_t \leftarrow B_t\right) \equiv p\left(A_t \vee \underline{B}_t\right) &\equiv \frac{\sum_{t=1}^{N}\left(A_t \vee \underline{B}_t\right)}{N} \equiv \frac{\left(A_t \vee \underline{B}_t\right) \times p\left(A_t \vee \underline{B}_t\right)}{\left(A_t \vee \underline{B}_t\right)} \\ &\equiv p\left(a_t\right) + p\left(b_t\right) + p\left(d_t\right) \\ &\equiv \frac{N \times \left(p\left(a_t\right) + p\left(b_t\right) + p\left(d_t\right)\right)}{N} \equiv \frac{E\left(A_t \leftarrow B_t\right)}{N} \\ &\equiv \frac{a+b+d}{N} \equiv \frac{E\left(A_t \vee \underline{B}_t\right)}{N} \\ &\equiv \frac{A+d}{N} \equiv \frac{E\left(A_t \leftarrow B_t\right)}{N} \\ &\equiv \frac{a+\underline{B}}{N} \equiv \frac{E\left(A_t \vee \underline{B}_t\right)}{N} \\ &\equiv +1 \end{aligned} \tag{101}$$

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

Remark 2.2. *A necessary condition A_t is characterised itself by the property that another event B_t will not occur if A_t is not given, if A_t did not occur (Barukčić, 1989, 1997, 2005, 2016b, 2017b,c,*

Table 6. Necessary condition.

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

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

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

$$\begin{aligned} p\left(A_t \leftarrow B_t\right) &\equiv +1 \\ &\equiv +1 - p\left(c_t\right) \\ &\equiv +1 - p\left(\underline{A}_t \cap B_t\right) \\ &\equiv \left(\int_{-\infty}^{A_t} \int_{-\infty}^{B_t} f\left(A_t, B_t\right)\, dA_t\, dB_t \right) + \left(1 - \int_{-\infty}^{B_t} f\left(B_t\right)\, dB_t \right) \end{aligned} \tag{102}$$

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

$$p\left(A_t \leftarrow B_t\right) \equiv \underbrace{\left(A_t \vee \underline{B}_t\right)}_{\text{(Nessessary condition)}} \equiv \underbrace{\left(\underline{B}_t \vee A_t\right)}_{\text{(Sufficient condition)}} \equiv p\left(B_t \rightarrow A_t\right) \tag{103}$$

There are circumstances under which

$$p\left(A_t \leftarrow B_t\right) \equiv \underbrace{\left(A_t \vee \underline{B}_t\right)}_{\text{(Nessessary condition)}} \equiv \underbrace{\left(\underline{A}_t \vee B_t\right)}_{\text{(Sufficient condition)}} \equiv p\left(A_t \rightarrow B_t\right) \tag{104}$$

However, equation 103 does not imply the relationship of equation 104 under any circumstances.

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

Definition 2.42 (**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

$$\begin{aligned} \tilde{\chi}^2{}_{\text{Calculated}}\left(A_\text{t} \leftarrow B_\text{t} \mid B\right) &\equiv \frac{\left(a-(a+c)\right)^2}{B}+ \\ &\quad \frac{\left((b+d)-\underline{B}\right)^2}{\underline{B}} \\ &\equiv \frac{c^2}{B}+0 \\ &\equiv \frac{c^2}{B} \end{aligned} \tag{105}$$

or equally as

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

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.

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

Definition 2.43 (**The left-tailed p Value of the conditio sine qua non relationship**).

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

lated as follows.

$$\begin{aligned} pValue_{\mathrm{lt}}\left(A_{\mathrm{t}} \leftarrow B_{\mathrm{t}}\right) &\equiv 1-e^{-\left(1-p\left(A_{\mathrm{t}} \leftarrow B_{\mathrm{t}}\right)\right)} \\ &\equiv 1-e^{-(c / N)} \end{aligned} \tag{107}$$

2.3.12. Sufficient condition

Definition 2.44 (**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

$$\begin{aligned} p\left(A_{\mathrm{t}} \rightarrow B_{\mathrm{t}}\right) \equiv p\left(\underline{A}_{\mathrm{t}} \vee B_{\mathrm{t}}\right) &\equiv \frac{\sum_{t=1}^{N}\left(\underline{A}_{\mathrm{t}} \vee B_{\mathrm{t}}\right)}{N} \equiv \frac{\left(\underline{A}_{\mathrm{t}} \vee B_{\mathrm{t}}\right) \times p\left(\underline{A}_{\mathrm{t}} \vee B_{\mathrm{t}}\right)}{\left(\underline{A}_{\mathrm{t}} \vee B_{\mathrm{t}}\right)} \\ &\equiv p\left(a_{\mathrm{t}}\right)+p\left(c_{\mathrm{t}}\right)+p\left(d_{\mathrm{t}}\right) \\ &\frac{N \times\left(p\left(a_{\mathrm{t}}\right)+p\left(c_{\mathrm{t}}\right)+p\left(d_{\mathrm{t}}\right)\right)}{N} \\ &\equiv \frac{a+c+d}{N} \equiv \frac{E\left(\underline{A}_{\mathrm{t}} \vee B_{\mathrm{t}}\right)}{N} \\ &\equiv \frac{B+d}{N} \equiv \frac{E\left(A_{\mathrm{t}} \rightarrow B_{\mathrm{t}}\right)}{N} \\ &\equiv \frac{a+\underline{A}}{N} \\ &\equiv+1 \end{aligned} \tag{108}$$

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 7). There are circumstances, where several different events might be necessary at the same time in order to determine a compound sufficient condition relationship. Equation 109 illustrates this case in more detail.

$$\begin{aligned} p\left(\left(\left({}_1X_{\mathrm{t}} \wedge {}_2X_{\mathrm{t}} \wedge {}_3X_{\mathrm{t}} \wedge \cdots\right) \wedge A_{\mathrm{t}}\right) \rightarrow B_{\mathrm{t}}\right) &\equiv p\left(\underline{\left(\left({}_1X_{\mathrm{t}} \wedge {}_2X_{\mathrm{t}} \wedge {}_3X_{\mathrm{t}} \wedge \cdots\right) \wedge A_{\mathrm{t}}\right)} \vee B_{\mathrm{t}}\right) \\ &\equiv \frac{\sum_{t=1}^{N}\left(\underline{\left(\left({}_1X_{\mathrm{t}} \wedge {}_2X_{\mathrm{t}} \wedge {}_3X_{\mathrm{t}} \wedge \cdots\right) \wedge A_{\mathrm{t}}\right)} \vee B_{\mathrm{t}}\right)}{N} \\ &\equiv+1 \end{aligned} \tag{109}$$

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

$$\begin{aligned} p\left(A_{\mathrm{t}} \rightarrow B_{\mathrm{t}}\right) &\equiv +1 \\ &\equiv +1-p\left(b_{\mathrm{t}}\right) \\ &\equiv +1-p\left(A_{\mathrm{t}} \cap \underline{B}_{\mathrm{t}}\right) \\ &\equiv \left(\int_{-\infty}^{A_{\mathrm{t}}} \int_{-\infty}^{B_{\mathrm{t}}} f\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right)\, dA_{\mathrm{t}}\, dB_{\mathrm{t}}\right)+\left(1-\int_{-\infty}^{A_{\mathrm{t}}} f\left(A_{\mathrm{t}}\right)\, dA_{\mathrm{t}}\right) \end{aligned} \tag{110}$$

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 7. Sufficient condition.

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

Remark 2.3. *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*

$$p\left(A_t \rightarrow B_t\right)+p\left(R_t \wedge B_t\right) \equiv +1 \tag{111}$$

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

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

Definition 2.45 (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 $\mathrm{p(A_t \rightarrow B_t)}$ 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

$$\begin{aligned}\tilde{\chi}^2{}_{\text{Calculated}}\left(A_{\text{t}} \rightarrow B_{\text{t}} \mid A\right) &\equiv \frac{\left(a-(a+b)\right)^2}{A}+ \\ &\quad \frac{\left((c+d)-\underline{A}\right)^2}{\underline{A}} \\ &\equiv \frac{b^2}{A}+0 \\ &\equiv \frac{b^2}{A}\end{aligned} \tag{112}$$

or equally as

$$\begin{aligned}\tilde{\chi}^2{}_{\text{Calculated}}\left(A_{\text{t}} \rightarrow B_{\text{t}} \mid \underline{B}\right) &\equiv \frac{\left(d-(b+d)\right)^2}{\underline{B}}+ \\ &\quad \frac{\left((a+c)-B\right)^2}{B} \\ &\equiv \frac{b^2}{\underline{B}}+0 \\ &\equiv \frac{b^2}{\underline{B}}\end{aligned} \tag{113}$$

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 $\text{p}(\text{A}_{\text{t}} \rightarrow \text{B}_{\text{t}})$, in which case the null hypothesis is accepted. Yate's (Yates, 1934) continuity correction has not been used in this context.

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

Definition 2.46 (The left-tailed p Value of the conditio per quam relationship).

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

$$\begin{aligned}pValue_{\text{lt}}\left(A_{\text{t}} \rightarrow B_{\text{t}}\right) &\equiv 1-e^{-\left(1-p\left(A_{\text{t}} \rightarrow B_{\text{t}}\right)\right)} \\ &\equiv 1-e^{-(b/N)}\end{aligned} \tag{114}$$

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

2.3.15. Necessary and sufficient conditions

Definition 2.47 (**Necessary and sufficient conditions [*EQV*]**).

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

$$\begin{aligned} p\left(A_t \leftrightarrow B_t\right) &\equiv \frac{\sum_{t=1}^{N}\left(\left(A_t \vee \underline{B}_t\right) \wedge \left(\underline{A}_t \vee B_t\right)\right)}{N} \\ &\equiv p\left(a_t\right) + p\left(d_t\right) \\ &\equiv \frac{N \times \left(p\left(a_t\right) + p\left(d_t\right)\right)}{N} \\ &\equiv \frac{a+d}{N} \\ &\equiv +1 \end{aligned} \tag{115}$$

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

Definition 2.48 (**The $\tilde{\chi}^2$ goodness of fit test of a necessary and sufficient condition relationship**).

Even the necessary and sufficient condition relationship $p(A_t \leftrightarrow B_t)$ 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

$$\begin{aligned} {\tilde{\chi}^2}_{\text{Calculated}}\left(A_t \leftrightarrow B_t \mid A\right) &\equiv \frac{\left(a-\left(a+b\right)\right)^2}{A} + \\ &\quad \frac{d-\left(\left(c+d\right)\right)^2}{\underline{A}} \\ &\equiv \frac{b^2}{A} + \frac{c^2}{\underline{A}} \end{aligned} \tag{116}$$

or equally as

$$\begin{aligned} {\tilde{\chi}^2}_{\text{Calculated}}\left(A_t \leftrightarrow B_t \mid B\right) &\equiv \frac{\left(a-\left(a+c\right)\right)^2}{B} + \\ &\quad \frac{d-\left(\left(b+d\right)\right)^2}{\underline{B}} \\ &\equiv \frac{c^2}{B} + \frac{b^2}{\underline{B}} \end{aligned} \tag{117}$$

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 $p(A_t \leftrightarrow B_t)$, the $\tilde{\chi}^2$-distribution equals zero. It is to be cleared whether Yate's (Yates, 1934) continuity correction should be used at all.

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

Definition 2.49 (The left-tailed p Value of a necessary and sufficient condition relationship).

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

$$\begin{aligned} pValue_{\mathrm{lt}}\left(A_t \leftrightarrow B_t\right) &\equiv 1 - e^{-(1-p(A_t \leftrightarrow B_t))} \\ &\equiv 1 - e^{-((b+c)/N)} \end{aligned} \tag{118}$$

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

Table 8. Necessary and sufficient condition.

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

2.3.18. Either or conditions

Definition 2.50 (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

$$\begin{aligned} p\left(A_t \succ\!\prec B_t\right) &\equiv \frac{\sum_{t=1}^{N}\left(\left(A_t \wedge \underline{B}_t\right) \vee \left(\underline{A}_t \wedge B_t\right)\right)}{N} \\ &\equiv p\left(b_t\right) + p\left(c_t\right) \\ &\equiv \frac{N \times \left(p\left(b_t\right) + p\left(c_t\right)\right)}{N} \\ &\equiv \frac{b+c}{N} \\ &\equiv +1 \end{aligned} \tag{119}$$

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

Table 9. Either A_t or B_t relationship.

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

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

Definition 2.51 (**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

$$\begin{aligned} \tilde{\chi}^2{}_{\text{Calculated}}\left(\left(A_t \succ\!\prec B_t\right) \mid A\right) &\equiv \frac{\left(b-(a+b)\right)^2}{A} + \\ &\quad \frac{c-\left((c+d)\right)^2}{\underline{A}} \\ &\equiv \frac{a^2}{A} + \frac{d^2}{\underline{A}} \end{aligned} \tag{120}$$

or equally as

$$\begin{aligned} \tilde{\chi}^2{}_{\text{Calculated}}\left(\left(A_t \succ\!\prec B_t\right) \mid B\right) &\equiv \frac{\left(c-(a+c)\right)^2}{B} + \\ &\quad \frac{b-\left((b+d)\right)^2}{\underline{B}} \\ &\equiv \frac{a^2}{B} + \frac{d^2}{\underline{B}} \end{aligned} \tag{121}$$

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

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

Definition 2.52 (**The left-tailed p Value of an either or condition relationship**).

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

$$\begin{aligned} pValue_{\mathrm{lt}}\left(A_{\mathrm{t}} \succ\!\!\prec B_{\mathrm{t}}\right) &\equiv 1 - e^{-(1-p(A_{\mathrm{t}}>-<B_{\mathrm{t}}))} \\ &\equiv 1 - e^{-((a+d)/N)} \end{aligned} \tag{122}$$

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

2.3.21. 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$^{\mathrm{th}}$ 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 2.53 (**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

$$\begin{aligned} k\left(U_t, W_t\right) &\equiv \frac{\sigma\left(U_t, W_t\right)}{\sigma\left(U_t\right) \times \sigma\left(W_t\right)} \\ &\equiv \frac{p\left(U_t \wedge W_t\right) - p\left(U_t\right) \times p\left(W_t\right)}{\sqrt[2]{\left(p\left(U_t\right) \times \left(1 - p\left(U_t\right)\right)\right) \times \left(p\left(W_t\right) \times \left(1 - p\left(W_t\right)\right)\right)}} \end{aligned} \tag{123}$$

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

Table 10. Sample space and the causal relationship k

		Effect B_t		
		TRUE	FALSE	
Cause 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.

2.3.22. Cause and effect

Definition 2.54 (Cause and effect).

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

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

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

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

$$(U_t \vee \underline{W}_t) \equiv (\underline{W}_t \vee U_t) \equiv ((U_t \vee \underline{W}_t) \wedge (\underline{W}_t \vee U_t)) \equiv +1 \tag{124}$$

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

$$(\underline{U}_t \vee W_t) \equiv (W_t \vee \underline{U}_t) \equiv ((\underline{U}_t \vee W_t) \wedge (W_t \vee \underline{U}_t)) \equiv +1 \tag{125}$$

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

$$(U_t \vee \underline{W}_t) \wedge (\underline{U}_t \vee W_t) \equiv +1 \tag{126}$$

However, I think it necessary to make a clear distinction between a necessary and sufficient condition and the converse relationship (Eq. 124) above.

$$((U_t \vee \underline{W}_t) \wedge (\underline{W}_t \vee U_t)) \neq (U_t \vee \underline{W}_t) \wedge (\underline{U}_t \vee W_t) \tag{127}$$

2.3.23. Statistical methods

The probability of the necessary (Barukčić, 2021c) condition p(SINE) has been calculated and tested for statistical significance. The probability of the sufficient (Barukčić, 2021c) condition p(IMP) has been calculated, the statistical significance of this relationship has been proofed. The chi-square goodness of fit test with one degree of freedom has been used to test whether the sample data published fit a certain theoretical distribution in the population. The causal relationship k (Barukčić, 2021c) has been calculated to evaluate a possible causal relationship between the events/factors analysed. The hyper-geometric(Fisher, 1922, Gonin, 1936, Huygens and van Schooten, 1657, Pearson, 1899) distribution (HGD) has been used to test the one-sided significance of the causal relationship k. Potential publication bias among the studies included is assessed by Begg's funnel plot [23] , [24] , [25] , [26] with a treatment effect (horizontal axis) and some measure of weight (inverse variance, standard error, sample

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size et cetera) on the vertical axis . 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 [27] , [28] , [29] . Under usual circumstances, an I^2 value of 25%, 50% and 75% are regarded as low, moderate and high heterogeneity[30]. In this publication, the study (design) bias and the heterogeneity among the studies has been controlled by IOI, the index of independence(Barukčić, 2019a) and IOU, the index of unfairness(Barukčić, 2019b). All the data were analysed using Microsoft Excel® version 14.0.7166.5000 (32 - Bit) software (Microsoft Corporation, USA). The p values less than 0.05 were considered to indicate a statistically significant difference.

2.4. Axioms

2.4.1. Axiom I. Lex identitatis

In this context, we define axiom I as the expression

$$+1 = +1 \tag{128}$$

2.4.2. Axiom II. Lex contradictionis

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

$$+0 = +1 \tag{129}$$

and equally the most simple form of a contradiction formulated.

2.4.3. Axiom III. Lex negationis

$$\neg(0) \times 0 = 1 \tag{130}$$

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

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3. Results

3.1. Re-analysis of the study of Jingtao Cui et al., 2018

Jingtao Cui et al. [31] investigated the age-dependent prevalence of different Epstein-Barr virus serological parameters in patients with various diseases. Cui et al. found and published that 94.91% or $\frac{5911}{Sample} \equiv 0.9491$ were EBV positive. The sample size follows as $Sample \equiv \frac{5911}{0.9491} \equiv 6228$. The prevalence of EBV VCA-IgG/EBNA1-IgG were treated as indicator of a past EBV infection. The data of Jingtao Cui et al. provided important evidence that the prevalence of EBV increased with age. In toto, 424/424 NPC patient were EBV VCA-IgG positive. Furthermore, 94.54 % or 5487/5804 non-nasopharyngeal carcinoma patients were EBV VCA-IgG positive. The data and the statistical analysis of the study of Jingtao Cui et al. are illustrated by table 12 in more detail.

Table 12. EBV IgG Pos. and NPC (Study Jingtao Cui et al., 2018).

		NPC		
		YES	NO	
EBV IgG Pos.	YES	424	5487	5911
	NO	0	317	317
		424	5804	6228

Statistical analysis.	
Causal relationship k =	+0,0625919350
p Value right tailed (HGD) =	0,0000000001
p (SINE) =	1,0000000000
$\tilde{\chi}^2$ (SINE — B_t) =	0,0000
$\tilde{\chi}^2$ (SINE — $\underline{A}_t$) =	0,0000
p Value right tailed (HGD) =	0,0000
p Value (SINE) =	0,0000000000
Relative risk (RR).	
RR (nc) =	**division by zero**
RR (sc) =	1,0578
Additional measures.	
OR =	0,1190
IOR =	+0,0536
Study design.	
p(IOU)=	0,017180475
p(IOI)=	0,881021195

[31] Cui J, Yan W, Xu S, Wang Q, Zhang W, Liu W, Ni A. Anti-Epstein-Barr virus antibodies in Beijing during 2013-2017: What we have found in the different patients. PLoS One. 2018 Mar 1;13(3):e0193171. doi: 10.1371/journal.pone.0193171. PMID: 29494658; PMCID: PMC5832223.

4. Discussion

The quality of data as presented by the study of Jingtao Cui et al. [32] with an index of unfairness [33] with $p(IOU) = 0,017180475$ is very impressive. In other words, the data are not biased and can be used to check the same data for a necessary [34] condition relationship. However, the index of independence [35] is equal to $p(IOI) = 0,881021195$ and indicates that the data of Jingtao Cui et al. should not be used to establish a cause-effect relationship between EBV and NPC. Nonetheless, the causal relationship k can be used to check the data for bias and self-contradictions. In the case of a significant necessary condition relationship, we should not obtain a (significant) negative causal relationship k. Indeed, the data of Jingtao Cui et al. yield a positive causal relationship k equal to $k(EBV,NPC) = +0,0625919350$. In other words, the data of Jingtao Cui et al. are neither biased nor self-contradictory. We can rely and work with these data. Under these assumptions, there is no way out but to accept that an Epstein–Barr virus infection is a necessary condition, a conditio sine qua non of nasopharyngeal carcinoma. In other words, **without** an EBV infection, **no** NPC.

In point of fact, the presence of EBV in nasopharyngeal carcinoma tumor cells can be investigated by various methods like different types of PCR [36, 37] technology, immunohistochemistry [38] (IHC), in situ hybridization (ISH) et cetera. In general, in situ hybridization is able to determine the absence or the presence of DNA or RNA sequences of interest and is able to localise these sequences to specific cells. Thus far, even a discrimination between cancer cells and lymphocytes [39] infiltrating a tumor cell is possible. However, it is to be noticed that several major steps like probe preparation and labeling, tissue fixation, permeabilization, hybridization, and signal detection et cetera are involved in 'in [40, 41, 42] situ hybridization'. Nonetheless, even ISH [43] methodology itself is prone to false-positive and to false-negative results.

Nevertheless, all these difficulties can in principle be overcome by performing comprehensively and

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accurately designed [44] clinical trials with minimum requirements outlined in detail as follows:

- $p(IOI) = 0,0$;
- *in situ hybridazation*[45,46,47,48,49] *methodology*;
- $control\ group: non-tumor\ part\ of\ the\ same\ specimen\ investigated.$

It is for precisely that reason that such a study should be able to provide us with a convincing evidence independently of the known *Henle(Henle, 1840) (1809–1885) - Koch(Koch, 1878) (1843–1910) postulates* (Carter, 1985) that an EBV infection is the cause of NPC.

5. Conclusion

Without Epstein–Barr virus infection, **no** nasopharyngeal carcinoma.

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6. Patient consent for publication

Not required.

Conflict of interest statement

No conflict of interest to declare.

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Private note

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

Erratum

None.

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