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Without a Varicella Zoster Virus Infection, no Schizophrenia

Research article

Ilija Barukčić[1]

[1] Internist, Horandstrasse, 26441 Jever, Germany

* **Correspondence:** E-Mail: Barukcic@t-online.de;
Tel: +49-4466-333; Fax: +49-4466-333.

Abstract

Background:

Despite decades of research and major efforts, a cause or the cause of schizophrenia is still not identified. Although many studies indicate that infectious agents are related to schizophrenia no definite consensus has been reached on this issue.

Methods:

The purpose of this study was to investigate relationship between varicella zoster virus (VZS) and schizophrenia while relying on new statistical methods.

Results:

The meta-analysis results provide striking evidence that VZV is a necessary condition of schizophrenia.

Conclusion:

There is some weak evidence that VZV infection is the cause of schizophrenia.

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

1. Introduction

Schizophrenia is a serious neuropsychiatric disorder characterized by various symptoms like hallucinations (i.e. hearing voices), delusions, paranoia, disorganized thinking, social withdrawal, decreased emotional expression et cetera. Schizophrenia is associated with increased mortality[1] , while the prevalence [2] , [3] of schizophrenia is estimated to be about 0.7%-1%. Several risk factors [4] including genetic factors, environmental exposures (winter-spring birth, urban birth, maternal pre-eclampsia, perinatal and postnatal infections et cetera) have been identified as increasing risk for schizophrenia. Even a potential role of infectious agents in the etiopathogenesis of schizophrenia has been discussed for

[1]Tanskanen A, Tiihonen J, Taipale H. Mortality in schizophrenia: 30-year nationwide follow-up study. Acta Psychiatr Scand. 2018 Dec;138(6):492-499. doi: 10.1111/acps.12913. Epub 2018 Jun 13. PMID: 29900527.

[2]van der Werf M, Hanssen M, Köhler S, Verkaaik M, Verhey FR; RISE Investigators, van Winkel R, van Os J, Allardyce J. Systematic review and collaborative recalculation of 133,693 incident cases of schizophrenia. Psychol Med. 2014 Jan;44(1):9-16. doi: 10.1017/S0033291712002796. Epub 2012 Dec 17. PMID: 23244442.

[3]Javitt DC. Balancing therapeutic safety and efficacy to improve clinical and economic outcomes in schizophrenia: a clinical overview. Am J Manag Care. 2014 Jun;20(8 Suppl):S160-5. PMID: 25180705.

[4]Radua J, Ramella-Cravaro V, Ioannidis JPA, Reichenberg A, Phiphopthatsanee N, Amir T, Yenn Thoo H, Oliver D, Davies C, Morgan C, McGuire P, Murray RM, Fusar-Poli P. What causes psychosis? An umbrella review of risk and protective factors. World Psychiatry. 2018 Feb;17(1):49-66. doi: 10.1002/wps.20490. PMID: 29352556; PMCID: PMC5775150.

decades. The French neurologist Jean Esquirol wrote: “Many authors assure us that mental alienation is epidemic. It is certain that there are years, when, independently of moral causes, insanity seems suddenly to extend to a great number of individuals.” (see Esquirol, 1845, p. 33) By time bacteria were becoming known and Theodore Deecke, the pathologist of the New York State Lunatic Asylum, suggested in 1874 in his article ‘On the Germ-Theory of Disease’ (see Deecke, 1874) by the American Journal of Insanity (now the American Journal of Psychiatry) an infectious hypothesis of schizophrenia too. Meanwhile, several articles [5] , including meta-analysis [6] of various infectious [7] agents in schizophrenia did not find convincing evidence of a causal relationship between schizophrenia and herpes simplex virus type 1 [8] (HSV-1), herpes simplex virus type 2 [9] (HSV-2), herpes simplex virus type 3 (HSV-3) or varicella-zoster [10] , [11] virus (VZV), herpes simplex virus type 4 (HSV-4) or Epstein-Barr [12] , [13] virus (EBV), herpes simplex virus type 5 (HSV-5) or cytomegalovirus [14] (CMV), Toxoplasma [15] gondii (TG) and other possible causes of encephalitis. Publication bias, con-founders and other factors contributed to contradicting results. Still, little is known about the etiology of schizophrenia, the etiology of schizophrenia remains uncertain. This unsatisfactory situation is aggravated by the fact that an objective diagnostic test (Diagnostic and Statistical Manual of Mental Disorders (DSM)) for schizophrenia is not given. It is not surprising that pharmacological and nonpharmacological treatments including psychosocial interventions and social supports for patients with schizophrenia are still unsatisfactory.

[5] Krause D, Matz J, Weidinger E, Wagner J, Wildenauer A, Obermeier M, Riedel M, Müller N. The association of infectious agents and schizophrenia. World J Biol Psychiatry. 2010 Aug;11(5):739-43. doi: 10.3109/15622971003653246. PMID: 20602604.

[6] Arias I, Sorlozano A, Villegas E, de Dios Luna J, McKenney K, Cervilla J, Gutierrez B, Gutierrez J. Infectious agents associated with schizophrenia: a meta-analysis. Schizophr Res. 2012 Apr;136(1-3):128-36. doi: 10.1016/j.schres.2011.10.026. Epub 2011 Nov 21. PMID: 22104141.

[7] Yolken RH, Torrey EF. Viruses, schizophrenia, and bipolar disorder. Clin Microbiol Rev. 1995 Jan;8(1):131-45. doi: 10.1128/CMR.8.1.131. PMID: 7704891; PMCID: PMC172852.

[8] Dickerson F, Schroeder JR, Nimgaonkar V, Gold J, Yolken R. The association between exposure to herpes simplex virus type 1 (HSV-1) and cognitive functioning in schizophrenia: A meta-analysis. Psychiatry Res. 2020 Sep;291:113157. doi: 10.1016/j.psychres.2020.113157. Epub 2020 Jun 21. PMID: 32593064.

[9] Mortensen PB, Pedersen CB, Hougaard DM, Nørgaard-Petersen B, Mors O, Børglum AD, Yolken RH. A Danish National Birth Cohort study of maternal HSV-2 antibodies as a risk factor for schizophrenia in their offspring. Schizophr Res. 2010 Sep;122(1-3):257-63. doi: 10.1016/j.schres.2010.06.010. Epub 2010 Jul 2. PMID: 20598509.

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[12] Barichello T, Badawy M, Pitcher MR, Saigal P, Generoso JS, Goularte JA, Simões LR, Quevedo J, Carvalho AF. Exposure to Perinatal Infections and Bipolar Disorder: A Systematic Review. Curr Mol Med. 2016;16(2):106-18. doi: 10.2174/1566524016666160126143741. PMID: 26812921.

[13] Dickerson F, Jones-Brando L, Ford G, Genovese G, Stallings C, Origoni A, O’Dushlaine C, Katsafanas E, Sweeney K, Khushalani S, Yolken R. Schizophrenia is Associated With an Aberrant Immune Response to Epstein-Barr Virus. Schizophr Bull. 2019 Sep 11;45(5):1112-1119. doi: 10.1093/schbul/sby164. PMID: 30462333; PMCID: PMC6737467.

[14] Li Y, Weber NS, Fisher JA, Yolken RH, Cowan DN, Larsen RA, Niebuhr DW. Association between antibodies to multiple infectious and food antigens and new onset schizophrenia among US military personnel. Schizophr Res. 2013 Dec;151(1-3):36-42. doi: 10.1016/j.schres.2013.10.004. Epub 2013 Oct 17. PMID: 24139899.

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1.1. Material

1.1.1. Literature search

A literature search was re-conducted using the electronic database PubMed until April 2, 2022. The keywords used for this systematic review were "varicella zoster virus"and "schizophrenia". The bibliographies of all articles obtained were also reviewed for additional relevant publications.

Reporting followed in adherence to Preferred Reporting [16] Items for Systematic Reviews and Meta-analysis(Liberati et al., 2009, Moher et al., 2009) as much as possible.

Table 1. *Systematic Reviews and Meta-analysis*

Identification:			
	PubMed		16
Screening:			
	Articles excluded I	13	
Eligibility:			
	Articles eligible for analysis		3
	Articles excluded II	2	
Inclusion:			
	Studies included (meta-analysis)		1

In general, several limiting factors (quality, availability, heterogeneity et cetera of the published data) like in all meta-analysis need to be considered before interpreting the results of a meta-analysis.

1.1.2. Inclusion and exclusion criteria

Studies were considered eligible for inclusion in the present meta-analysis, if they met the following criteria:

(1) Studies, including reviews, published in the English language.

(2) Studies using a case-control design.

(3) Studies without data access barrier. For various reasons, it was not possible to consider studies with data access barriers. The abstract should contain all the information needed, alternatively free full text access to the article was necessary.

[16] Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009 Aug 18;151(4):264-9, W64. doi: 10.7326/0003-4819-151-4-200908180-00135. Epub 2009 Jul 20. PMID: 19622511.

(5) Case reports, letters, conference abstracts, or expert opinions were excluded and not considered.

1.1.3. Study selection and characteristics

The literature search yielded 16 potentially eligible titles. The abstracts were reviewed, inappropriate articles were excluded and removed. At the end, 1 article which met the inclusion criteria was eligible for meta-analyses.

1.1.4. Data extraction and assessment of study quality

Data were extracted in a pre-designed data extraction form using Microsoft Excel 2013 (Microsoft Corporation, Redmond, Washington, USA) and statistically analysed.

1.1.5. Statistical methods

The probability of the necessary (Barukčić, 2021c) condition p(SINE) has been calculated and tested for statistical significance. The chi-square goodness of fit test with one degree of freedom has been used to test whether the sample data published fit a certain theoretical distribution in the population. 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. In general, potential publication bias among the studies included is assessed by Begg's funnel plot [17] , [18] , [19] , [20] with a treatment effect (horizontal axis) and some measure of weight (inverse variance, standard error, sample size et cetera) on the vertical axis. Indeed, bringing different studies together for analysing them or doing a meta-analysis is not without problems. Due to several reasons,a variability in the data of the studies is possible and there might be differences found. Usually, the heterogeneity among studies is assessed through I^2 statistics [21] , [22] , [23] . Under usual circumstances, an I^2 value of 25%, 50% and 75% are regarded as low, moderate and high heterogeneity[24]. In this publication, study (design) bias and heterogeneity has been controlled by

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

[18] 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.

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

[20] 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.

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

[22] 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.

[23] 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.

[24] 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.

IOI, the index of independence(Barukčić, 2019c) and IOU, the index of unfairness(Barukčić, 2019d). The p values less than 0.05 were considered to indicate a statistically significant difference.

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. Methods

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

2.1.1. Random variables

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

2.1.1.1. The Expectation of a Random Variable

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

$$\begin{aligned} E(X) &\equiv X \times p(X) \\ &\equiv \Psi(X) \times X \times \Psi^{*}(X) \end{aligned} \tag{1}$$

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 1 (see p. 10) becomes

$$E(X) \equiv X \tag{2}$$

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

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

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:

$$E\left(X_{kl\mu\nu\dots}\right) \equiv p\left(X_{kl\mu\nu\dots}\right) \times X_{kl\mu\nu\dots} \equiv p\left(X_{kl\mu\nu\dots}\right) \cap X_{kl\mu\nu\dots} \tag{4}$$

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

$$\begin{aligned} {}^2E\left(X_{kl\mu\nu\dots}\right) &\equiv p\left(X_{kl\mu\nu\dots}\right) \times X_{kl\mu\nu\dots} \times p\left(X_{kl\mu\nu\dots}\right) \times X_{kl\mu\nu\dots} \\ &\equiv p\left(X_{kl\mu\nu\dots}\right) \times p\left(X_{kl\mu\nu\dots}\right) \times X_{kl\mu\nu\dots} \times X_{kl\mu\nu\dots} \\ &\equiv {}^2\left(p\left(X_{kl\mu\nu\dots}\right) \times X_{kl\mu\nu\dots}\right) \\ &\equiv E\left(X_{kl\mu\nu\dots}\right) \times E\left(X_{kl\mu\nu\dots}\right) \end{aligned} \tag{5}$$

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

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

From the point of view of tensor algebra it is

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

Definition 2.3 (**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:*

$$\begin{aligned} E\left(X^{n}\right) &\equiv p\left(X\right) \times X^{n} \\ &\equiv \left(p\left(X\right) \times X\right) \times X^{n\text{-}1} \\ &\equiv E\left(X\right) \times X^{n\text{-}1} \end{aligned} \tag{8}$$

2.1.1.2. Probability of a Random Variable What is the nature of the probability of an event, or what is the relationship between probability and geometry or between the probability of an event and notions like false or true. At a first pass, various authors answer this question, one way or another. For authors like De Morgan, probability is only a degree of confidence, or credences or of belief. "By degree of probability, we really mean, or ought to mean, degree of belief" (see De Morgan, 1847, p. 172). Such a purely subjective (or personalist or Bayesian (see Bayes, 1763)) interpretation of probabilities as degrees of confidence, or credences finds its own scientific opposition, moreover, in Kolmogorov's axiomatization of probability theory. However, perhaps we can do better, then, to think that Kolmogorov's axiomatization of probability theory is the last word spoken on probability theory. Nobody seriously considers that Kolmogorov's conceptual apparatus of probability theory has solved the basic problem of any probability theory, the relationship between classical logic or geometry and probability theory. One very massive disadvantage of Kolmogorov's axiomatization of probability theory is that it is very silent especially on this issue. Any unification of geometry and probability theory into one unique mathematical framework might prove very difficult as long as we rely purely on Kolmogorov's understanding of probability theory. It's not surprising that the probability of an event bear at least directly, and sometimes indirectly, upon central philosophical and scientific concerns. A correct understanding of probability is one of the most important foundational scientific problems. Now let us strengthen our position with respect to the probability of an event. In our understanding, the probability of an event is something objectively and real. The probability of an event is the truth value of something or the degree to which something, i.e. a random variable X, is determined by its own expectation value. The probability p(X) of a random variable X follows as (see equation 1)

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

where $\Psi(X)$ is the wave-function of X, $\Psi^{*}(X)$ is the complex conjugate wave-function of X. In our understanding, conditions are possible where the elementary relationship between geometry (i.e. Pythagorean theorem, Euclid's theorem et cetera) and probability theory / statistics (see also figure 1) is given by the equation:

$$a^{2} \equiv E\left(X^{2}\right) \tag{10}$$

Further research should be able and might provide convincing evidence whether - and to what extent - equation 10 makes any sense at all. However, none of this relieves us of our duty to seriously consider the possibility of negative probabilities (see theorem 3.38 Barukčić, 2019b, pp. 67-68) like

$$-p(X) \equiv \frac{-E(X)}{-X} \tag{11}$$

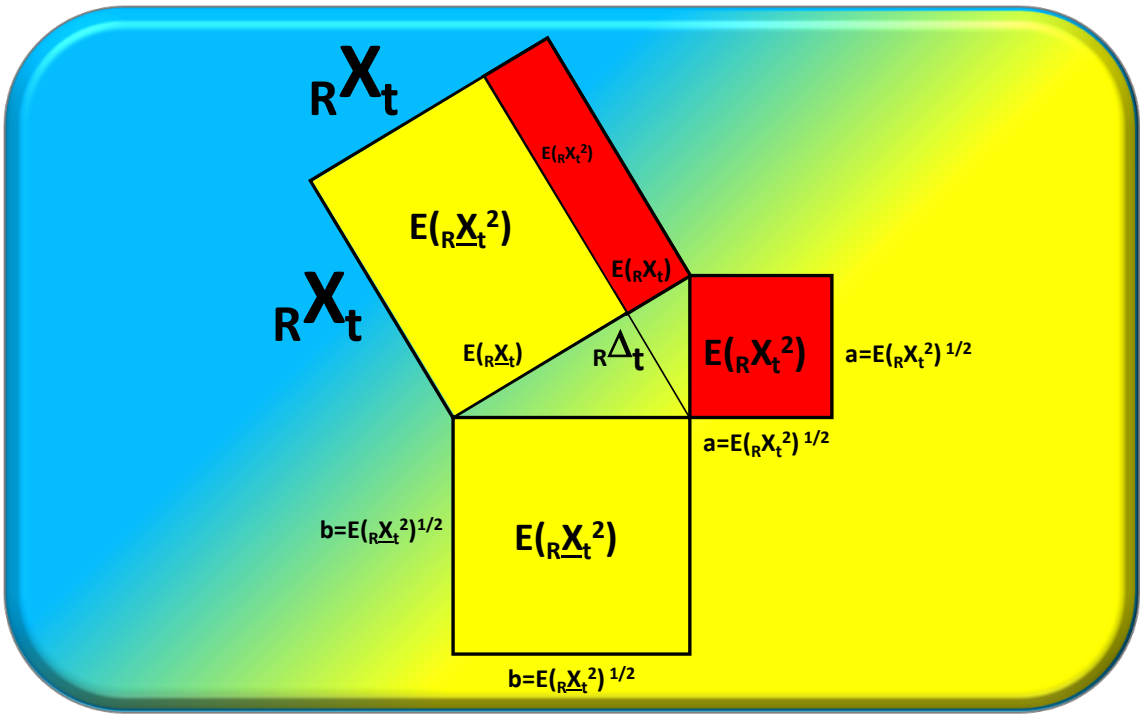

Figure 1. Geometry and probability theory.

An undeniable consequence of the previous explanations is that the "local hidden variable" (see Bohm, 1952, De Broglie, Louis, 1927), denoted as $E(\underline{X})$, is determined by the relationship

$$E(\underline{X}) \equiv \frac{\sigma(X)^{2}}{E(X)} \equiv \frac{\sigma(X)^{2}}{\Psi(X) \times X \times \Psi^{*}(X)} \tag{12}$$

From the point of view of tensor algebra, we obtain

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

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

2.1.1.3. Variance of a Random Variable

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

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

The deviation of a random variable X from its population mean or sample mean E(X) has a central role in statistics and is one important measure of dispersion. The variance $\sigma(X)^2$ (see Kolmogorov, 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 6):

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

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

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

All things considered, we can safely say that, on the whole, **the variance is a mathematical description of the philosophical notion of the inner contradiction of a random variable X** (see Hegel, Georg Wilhelm Friedrich, 1812a, 1813, 1816) . Based on equation 14, it is

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

or

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

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

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

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

[25] 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 2.5 (**The First Moment Expectation of a Random Variable of $\underline{X}$ (anti X)**). *In general, let $E(\underline{X})$ be defined as*

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

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

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

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

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

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

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

Definition 2.6 (**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 2.7 (**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 2.8 (**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

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

2.1.2. Bernoulli distribution

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

Definition 2.9 (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

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

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

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

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

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

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

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

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

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

In general, it is

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

Table 2 provide us with an overview of the definitions above.

In our understanding, it is

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

Table 2. 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 '.

2.1.3. Binomial random variables

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

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

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

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

or as

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

Furthermore, it is

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

or

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

The binomial distribution is the mathematical foundation of a binomial test. The random variable X_t is counting for different things. The discrete geometric (see Feller, 1950, p. 61) distribution describes under certain circumstances the number of Bernoulli trials needed to get one success. The probability

that the first occurrence of success requires k independent trials, each with success probability p, is given by the equation

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

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

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

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

Definition 2.10 (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 2.11 (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 3 provide us again an overview of a two by two table of Binomial random variables.

Table 3. The two by two table of Binomial random variables

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

2.1.4. Independence

Definition 2.12 (Independence).

The philosophical, mathematical(Kolmogoroff, Andreĭ Nikolaevich, 1933) and physical(Einstein, 1948) et cetera concept of independence is of fundamental(Kolmogoroff, Andreĭ Nikolaevich, 1933) importance in (natural) sciences as such. Therefore, it is appropriate to investigate the concept of independence as completely as possible. In fact, it is insightful to recall again before the mind's eye Einstein's theoretical approach to the concept of independence. "*Ohne die Annahme einer ... Unabhängigkeit der ... Dinge voneinander ... wäre physikalisches Denken ... nicht möglich.*"(Einstein, 1948). In a narrower sense, the conditio sine qua non relationship concerns itself at the end only with the case whether the presence of an event A_t (condition) enables or guarantees the presence of another event B_t (conditioned). 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), in terms of probability theory, independence (Kolmogoroff, Andreĭ Nikolaevich, 1933) of events at the same (period of) time (i.e. Bernoulli trial) t is defined as

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

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

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

or

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

and

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

Example. As a result of the thoughts before, another question worth asking concerns the relationship between the independence of an event A_t (a condition) and another event B_t (conditioned) and the necessary condition relationship. To be confronted with the danger of bias and equally with the burden of inappropriate conclusions drawn, another fundamental question at this stage is whether is it possible that an event A_t (a condition) is a necessary condition of event B_t (conditioned) even under circumstances where the event A_t (a condition) (a necessary condition) is independent of an event B_t (conditioned)? Meanwhile, this question is more or less already answered to the negative (Barukčić, 2018b). An event A_t which is a necessary condition of another event B_t is equally an event without which another event (B_t) could not be, could not occur, and implies as such already a kind of dependence. However, it is not mandatory that such a kind of dependence is a causal one. It is remarkable that **data which provide evidence of a significant conditio sine qua non relationship between two events like A_t and B_t and equally support the hypothesis that A_t and B_t are independent of each other are more or less self-contradictory and of very restricted or of none value for further analysis**. In fact, if the opposite view would be taken as plausible, contradictions are more or less inescapable.

2.1.5. Dependence

Definition 2.13 (Dependence).

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

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

2.1.6. Sensitivity and specificity

Definition 2.14 (Sensitivity and specificity)**.**

A (medical) test should measure what is supposed to measure. However, the extent to which a test measures what it is supposed to measure varies and is seldom equal to 100 %. In other words, it is necessary to check once and again the accuracy or the validity of a test, we have to fight it out in detail. In clinical practice, the concept of sensitivity and specificity is commonly used to quantify the diagnostic ability of a (medical) test. Sensitivity and specificity were introduced by the American [26] , [27] , [28] , [29] biostatistician Jacob Yerushalmy (see also Yerushalmy, 1947) in the year 1947. The interior logic of sensitivity and specificity is best illustrated using a conventional two- by-two (2 x 2) table (see table 4).

Table 4. Sensitivity and specificity

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

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

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

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

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

The positive predictive value (PPV) is defined as

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

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

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

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

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

The negative predictive value (NPV) is defined as

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

Example.

The importance of sensitivity and specificity in any research should certainly not be underestimated. However, it is essential not to lose sight of the major advantages and limitations [30] of these measures. In the following, in order to avoid misconceptions about sensitivity, specificity et cetera, let us consider a test with a sensitivity of 95 % and a specificity of 95 %. A two-by-two table is used as an illustration (see table 5).

Table 5. Sensitivity and specificity

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

Sensitivity is calculated as

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

There are at least two kinds of medical tests, diagnostic tests and screening tests. Depending on the type of medical test, there are other logical implications. A screening test should correctly identify all people who suffer from a certain disease or all people with a certain outcome. Therefore, the sensitivity of a screening test should be at best 100 %. Under these conditions, we obtain **without** positive test **no** disease/outcome present. However, confusion should be avoided with regard to the adequacy and usefulness of the sensitivity of a screening test. The sensitivity of a test does not take into account events which are false positive (b) or which are true negative (d), the meaning of these events is ignored completely by sensitivity. Therefore, sensitivity is blind on one eye since its inception and underestimates the extent to which a screening test is able to identify the likely presence of a condition of interest. We calculated a 95 % sensitivity while the true possibility of the test to detect a disease is (see table 5)

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

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

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

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

However, specificity does not take into account any individuals who suffer from a disease, who do have the condition and is well-known for being imperfect because of this fact too. Specificity underestimates the possibility of a diagnostic test to detect a disease. Above, the specificity has been calculated as being 95 %. In point of fact, the ability of the test to detect a disease or the relationship **if** test positive **then** disease present is much better and has to be calculated as (see table 5)

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

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

2.1.7. Odds ratio (OR)

Definition 2.15 (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 6. The odds' ratio (OR) is defined as

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

Table 6. 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

Remark 2.1. *Odds ratios can support logical fallacies and cause difficulties in drawing logically consistent conclusions. The chorus of voices is growing, which demand the immediate ending(Knol, 2012, Sackett, DL and Deeks, JJ and Altman, DG, 1996) of any use of Odds ratio.*

Under conditions where (b = 0), the measure of association odds ratio will collapse, because we need to divide by zero, as can be seen at eq. 78. However, according to today's rules of mathematics, a division by zero is neither allowed nor generally accepted as possible. It does no harm to remind ourselves that in the case b = 0 the event A_t is a sufficient condition of B_t. In other words, odds ratio is not able to recognize elementary relationships of objective reality. In fact, it would be a failure not to recognize how dangerous and less valuable odds ratio is.

Under conditions where (c = 0) odds ratio collapses too, because we need again to divide by zero, as can be seen at eq. 78. However, and again, today's rules of mathematics don't allow us a division by zero. In point of fact, in the case c = 0 it is more than necessary to point out that A_t is a necessary condition of B_t. In other words, odds ratio or the cross-product ratio is not able to recognize elementary relationships of nature like necessary conditions. We can and need to overcome all the epistemological obstacles as backed by odds ratio entirety. Sooner rather than later, we should give up this measure of relationship completely.

2.1.8. Relative risk (RR)

2.1.8.1. Relative risk (RR_{nc})

Definition 2.16 (Relative risk (RR_{nc}))**.**

The degree of association between the two binomial variables can be assessed by a number of very different coefficients, the relative (Cornfield, 1951, Sadowsky et al., 1953) risk is one(Barukčić, 2021d) of them. In general, relative risk RR_{nc}, which provides some evidence of a necessary condition, is defined as

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

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

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

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

2.1.8.2. Relative risk (RR (sc))

Definition 2.17 (Relative risk (RR (sc)))**.**

The relative risk (sc), which provides some evidence of a sufficient condition, is calculated from the

point of view of an outcome and is defined as

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

2.1.8.3. Relative risk reduction (RRR)

Definition 2.18 (Relative risk reduction (RRR))**.**

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

2.1.8.4. Vaccine efficacy (VE)

Definition 2.19 (Vaccine efficacy (VE))**.**

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

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

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

2.1.8.5. Experimental event rate (EER)

Definition 2.20 (Experimental event rate (EER))**.**

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

Definition 2.21 (Control event rate (CER))**.**

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

2.1.8.6. Absolute risk reduction (ARR)

Definition 2.22 (Absolute risk reducation (ARR))**.**

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

2.1.8.7. Absolute risk increase (ARI)

Definition 2.23 (Absolute risk increase (ARI))**.**

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

2.1.8.8. Number needed to treat (NNT)

Definition 2.24 (Number needed to treat (NNT))**.**

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

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

2.1.8.9. Number needed to harm (NNH)

Definition 2.25 (Number needed to harm (NNH))**.**

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

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

2.1.8.10. Outcome prevalence rate (OPR)

Definition 2.26 (Outcome prevalence rate (OPR))**.**

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

2.1.8.11. Control prevalence rate (CPR)

Definition 2.27 (Control prevalence rate (CPR))**.**

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

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

2.1.8.12. Absolute prevalence reduction (APR)

Definition 2.28 (Absolute prevalence reduction (APR))**.**

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

2.1.8.13. Absolute prevalence increase (API)

Definition 2.29 (Absolute prevalence increase (API))**.**

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

2.1.8.14. Relative prevalence reduction (RPR)

Definition 2.30 (Relative prevalence reduction (RPR))**.**

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

2.1.8.15. The index NNS

Definition 2.31 (The index NNS)**.**

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

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

2.1.8.16. The index NNI

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

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

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

2.1.9. Study design and bias

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

2.1.9.1. Index of unfairness (IOU)

Definition 2.33 (Index of unfairness).

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

$$p\left(IOU\left(A,B\right)\right) \equiv Absolute\left(\left(\frac{A+B}{N}\right)-1\right) \tag{96}$$

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.

2.1.9.2. Index of independence (IOI)

Definition 2.34 (Index of independence).

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

$$p\left(IOI\left(A_{\mathrm{t}},\underline{B}_{\mathrm{t}}\right)\right) \equiv Absolute\left(\left(\frac{A_{\mathrm{t}}+\underline{B}_{\mathrm{t}}}{N}\right)-1\right) \tag{97}$$

or as

$$p\left(IOI\left(\underline{A}_{\mathrm{t}},B_{\mathrm{t}}\right)\right) \equiv Absolute\left(\left(\frac{\underline{A}_{\mathrm{t}}+B_{\mathrm{t}}}{N}\right)-1\right) \tag{98}$$

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.

2.1.9.3. Index of relationship (IOR)

Definition 2.35 (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

$$\begin{aligned} IOR(A_t, B_t) &\equiv \left(\frac{p(A_t \wedge B_t)}{p(B_t) \times p(A_t)} \right) - 1 \\ &\equiv \left(\frac{p(a_t)}{p(B_t) \times p(A_t)} \right) - 1 \\ &\equiv \left(\left(\frac{N \times N \times p(a_t)}{N \times p(B_t) \times N \times p(A_t)} \right) - 1 \right) \\ &\equiv \left(\left(\frac{N \times a}{A \times B} \right) - 1 \right) \end{aligned} \tag{99}$$

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

2.2. Conditions

2.2.1. Exclusion relationship

Definition 2.36 (**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

$$\begin{aligned} p(A_t \mid B_t) &\equiv p(A_t \uparrow B_t) \\ &\equiv p(b_t) + p(c_t) + p(d_t) \\ &\equiv \frac{N \times (p(b_t) + p(c_t) + p(d_t))}{N} \\ &\equiv \frac{\sum_{t=1}^{N} (\underline{A}_t \vee \underline{B}_t)}{N} \equiv \frac{b+c+d}{N} \\ &\equiv \frac{b+\underline{A}}{N} \\ &\equiv \frac{c+\underline{B}}{N} \\ &\equiv +1 \end{aligned} \tag{100}$$

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 7).

Table 7. 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.*

$$\begin{aligned} p(Vaccine : BNT162b2 \mid COVID-19(infection)) &\equiv p(b_t) + p(c_t) + p(d_t) \\ &\equiv 1 - p(a_t) \\ &\equiv 1 - \left(\frac{8}{43538}\right) \\ &\equiv +0,99981625 \end{aligned} \tag{101}$$

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

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

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

2.2.2. Observational study and exclusion relationship

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

$$p\left(A_t \mid B_t\right) \equiv p\left(A_t \uparrow B_t\right) \geq 1 - \frac{p\left(a_t\right)}{p\left(B_t\right)} \tag{103}$$

2.2.3. Experimental study and exclusion relationship

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

$$p\left(A_t \mid B_t\right) \equiv p\left(A_t \uparrow B_t\right) \geq 1 - \frac{p\left(a_t\right)}{p\left(A_t\right)} \tag{104}$$

2.2.4. The goodness of fit test of an exclusion relationship

Definition 2.37 (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

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

or equally as

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

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

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

Definition 2.38 (**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, 2019e) of an exclusion relationship can be calculated as follows.

$$\begin{aligned}pValue_{\text{lt}}\left(A_{\text{t}} \mid B_{\text{t}}\right) &\equiv 1-e^{-(1-p(A_{\text{t}}|B_{\text{t}}))} \\ &\equiv 1-e^{-(a/N)}\end{aligned} \tag{107}$$

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

2.2.6. Neither nor conditions

Definition 2.39 (**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

$$\begin{aligned} p\left(A_t \downarrow B_t\right) &\equiv p\left(d_t\right) \\ &\equiv \frac{N - \sum_{t=1}^{N} \left(A_t \vee B_t\right)}{N} \equiv \frac{\sum_{t=1}^{N} \left(\underline{A}_t \wedge \underline{B}_t\right)}{N} \equiv \frac{N \times \left(p\left(d_t\right)\right)}{N} \\ &\equiv \frac{d}{N} \\ &\equiv +1 \end{aligned} \tag{108}$$

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

Definition 2.40 (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

$$\begin{aligned} {\tilde{\chi}^2}_{\text{Calculated}}\left(\left(A_t \downarrow B_t\right) \mid A\right) &\equiv \frac{\left(d - \left(c + d\right)\right)^2}{\underline{A}} + \\ &\quad \frac{\left(\left(a + b\right) - A\right)^2}{A} \\ &\equiv \frac{c^2}{\underline{A}} + 0 \end{aligned} \tag{109}$$

or equally as

$$\begin{aligned} {\tilde{\chi}^2}_{\text{Calculated}}\left(\left(A_t \downarrow B_t\right) \mid B\right) &\equiv \frac{\left(d - \left(b + d\right)\right)^2}{\underline{B}} + \\ &\quad \frac{\left(\left(a + c\right) - B\right)^2}{B} \\ &\equiv \frac{b^2}{\underline{B}} + 0 \end{aligned} \tag{110}$$

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

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

Definition 2.41 (The left-tailed p Value of a neither A_t nor B_t condition relationship).

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

$$\begin{aligned} pValue_{\mathrm{lt}}\left(A_{\mathrm{t}} \downarrow B_{\mathrm{t}}\right) &\equiv 1 - e^{-(1-p(A_{\mathrm{t}} \downarrow B_{\mathrm{t}}))} \\ &\equiv 1 - e^{-p(A_{\mathrm{t}} \vee B_{\mathrm{t}})} \\ &\equiv 1 - e^{-((a+b+c)/N)} \end{aligned} \tag{111}$$

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 $p\left(A_{\mathrm{t}} \vee B_{\mathrm{t}}\right) \equiv 1 - p\left(A_{\mathrm{t}} \downarrow B_{\mathrm{t}}\right)$ (see table 8).

Table 8. Neither A_t nor B_t relationship.

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

2.2.9. Necessary condition

Definition 2.42 (**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

$$\begin{aligned} p\left(A_t \leftarrow B_t\right) \equiv p\left(A_t \vee \underline{B}_t\right) &\equiv \frac{\sum_{t=1}^{N}\left(A_t \vee \underline{B}_t\right)}{N} \equiv \frac{\left(A_t \vee \underline{B}_t\right) \times p\left(A_t \vee \underline{B}_t\right)}{\left(A_t \vee \underline{B}_t\right)} \\ &\equiv p\left(a_t\right) + p\left(b_t\right) + p\left(d_t\right) \\ &\equiv \frac{N \times \left(p\left(a_t\right) + p\left(b_t\right) + p\left(d_t\right)\right)}{N} \equiv \frac{E\left(A_t \leftarrow B_t\right)}{N} \\ &\equiv \frac{a+b+d}{N} \equiv \frac{E\left(A_t \vee \underline{B}_t\right)}{N} \\ &\equiv \frac{A+d}{N} \equiv \frac{E\left(A_t \leftarrow B_t\right)}{N} \\ &\equiv \frac{a+\underline{B}}{N} \equiv \frac{E\left(A_t \vee \underline{B}_t\right)}{N} \\ &\equiv +1 \end{aligned} \tag{112}$$

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 9).

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 9. 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

$$\begin{aligned} p\left(A_t \leftarrow B_t\right) &\equiv +1 \\ &\equiv +1 - p\left(c_t\right) \\ &\equiv +1 - p\left(\underline{A}_t \cap B_t\right) \\ &\equiv \left(\int_{-\infty}^{A_t} \int_{-\infty}^{B_t} f\left(A_t, B_t\right)\, dA_t\, dB_t \right) + \left(1 - \int_{-\infty}^{B_t} f\left(B_t\right)\, dB_t \right) \end{aligned} \tag{113}$$

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

$$p\left(A_t \leftarrow B_t\right) \equiv \underbrace{\left(A_t \vee \underline{B}_t\right)}_{\text{(Nessessary condition)}} \equiv \underbrace{\left(\underline{B}_t \vee A_t\right)}_{\text{(Sufficient condition)}} \equiv p\left(B_t \rightarrow A_t\right) \tag{114}$$

There are circumstances under which

$$p\left(A_t \leftarrow B_t\right) \equiv \underbrace{\left(A_t \vee \underline{B}_t\right)}_{\text{(Nessessary condition)}} \equiv \underbrace{\left(\underline{A}_t \vee B_t\right)}_{\text{(Sufficient condition)}} \equiv p\left(A_t \rightarrow B_t\right) \tag{115}$$

However, equation 114 does not imply the relationship of equation 115 under any circumstances.

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

Definition 2.43 (**The $\tilde{\chi}^2$ goodness of fit test of a necessary condition relationship**).

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

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

or equally as

$$\begin{aligned} {\tilde{\chi}^2}_{\text{Calculated}}\left(A_t \leftarrow B_t \mid \underline{A}\right) &\equiv \frac{\left(d-(c+d)\right)^2}{\underline{A}}+ \\ &\quad \frac{\left((a+b)-A\right)^2}{A} \\ &\equiv \frac{c^2}{\underline{A}}+0 \\ &\equiv \frac{c^2}{\underline{A}} \end{aligned} \tag{117}$$

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

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

Definition 2.44 (**The left-tailed p Value of the conditio sine qua non relationship**).

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

lated as follows.

$$\begin{aligned} pValue_{\mathrm{lt}}\left(A_{\mathrm{t}} \leftarrow B_{\mathrm{t}}\right) &\equiv 1-e^{-\left(1-p\left(A_{\mathrm{t}} \leftarrow B_{\mathrm{t}}\right)\right)} \\ &\equiv 1-e^{-(c/N)} \end{aligned} \tag{118}$$

2.2.12. Sufficient condition

Definition 2.45 (**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

$$\begin{aligned} p\left(A_{\mathrm{t}} \rightarrow B_{\mathrm{t}}\right) \equiv p\left(\underline{A}_{\mathrm{t}} \vee B_{\mathrm{t}}\right) &\equiv \frac{\sum_{t=1}^{N}\left(\underline{A}_{\mathrm{t}} \vee B_{\mathrm{t}}\right)}{N} \equiv \frac{\left(\underline{A}_{\mathrm{t}} \vee B_{\mathrm{t}}\right) \times p\left(\underline{A}_{\mathrm{t}} \vee B_{\mathrm{t}}\right)}{\left(\underline{A}_{\mathrm{t}} \vee B_{\mathrm{t}}\right)} \\ &\equiv p\left(a_{\mathrm{t}}\right)+p\left(c_{\mathrm{t}}\right)+p\left(d_{\mathrm{t}}\right) \\ &\frac{N \times\left(p\left(a_{\mathrm{t}}\right)+p\left(c_{\mathrm{t}}\right)+p\left(d_{\mathrm{t}}\right)\right)}{N} \\ &\equiv \frac{a+c+d}{N} \equiv \frac{E\left(\underline{A}_{\mathrm{t}} \vee B_{\mathrm{t}}\right)}{N} \\ &\equiv \frac{B+d}{N} \equiv \frac{E\left(A_{\mathrm{t}} \rightarrow B_{\mathrm{t}}\right)}{N} \\ &\equiv \frac{a+\underline{A}}{N} \\ &\equiv +1 \end{aligned} \tag{119}$$

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 10). There are circumstances, where several different events might be necessary at the same time in order to determine a compound sufficient condition relationship. Equation 120 illustrates this case in more detail.

$$\begin{aligned} p\left(\left(\left({}_1X_{\mathrm{t}} \wedge {}_2X_{\mathrm{t}} \wedge {}_3X_{\mathrm{t}} \wedge \cdots\right) \wedge A_{\mathrm{t}}\right) \rightarrow B_{\mathrm{t}}\right) &\equiv p\left(\underline{\left(\left({}_1X_{\mathrm{t}} \wedge {}_2X_{\mathrm{t}} \wedge {}_3X_{\mathrm{t}} \wedge \cdots\right) \wedge A_{\mathrm{t}}\right)} \vee B_{\mathrm{t}}\right) \\ &\equiv \frac{\sum_{t=1}^{N}\left(\underline{\left(\left({}_1X_{\mathrm{t}} \wedge {}_2X_{\mathrm{t}} \wedge {}_3X_{\mathrm{t}} \wedge \cdots\right) \wedge A_{\mathrm{t}}\right)} \vee B_{\mathrm{t}}\right)}{N} \\ &\equiv +1 \end{aligned} \tag{120}$$

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

$$\begin{aligned} p\left(A_{\mathrm{t}} \rightarrow B_{\mathrm{t}}\right) &\equiv +1 \\ &\equiv +1-p\left(b_{\mathrm{t}}\right) \\ &\equiv +1-p\left(A_{\mathrm{t}} \cap \underline{B}_{\mathrm{t}}\right) \\ &\equiv \left(\int_{-\infty}^{A_{\mathrm{t}}} \int_{-\infty}^{B_{\mathrm{t}}} f\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right)\, dA_{\mathrm{t}}\, dB_{\mathrm{t}}\right)+\left(1-\int_{-\infty}^{A_{\mathrm{t}}} f\left(A_{\mathrm{t}}\right)\, dA_{\mathrm{t}}\right) \end{aligned} \tag{121}$$

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 10. Sufficient condition.

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

Remark 2.3. *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*

$$p\left(A_t \rightarrow B_t\right)+p\left(R_t \wedge B_t\right) \equiv +1 \tag{122}$$

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

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

Definition 2.46 (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 $\mathrm{p}(\mathrm{A_t} \rightarrow \mathrm{B_t})$ 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

$$\begin{aligned}\tilde{\chi}^2{}_{\text{Calculated}}\left(A_{\text{t}} \rightarrow B_{\text{t}} \mid A\right) &\equiv \frac{\left(a-(a+b)\right)^2}{A}+ \\ &\quad \frac{\left((c+d)-\underline{A}\right)^2}{\underline{A}} \\ &\equiv \frac{b^2}{A}+0 \\ &\equiv \frac{b^2}{A}\end{aligned} \tag{123}$$

or equally as

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

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.

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

Definition 2.47 (The left-tailed p Value of the conditio per quam relationship).

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

$$\begin{aligned}pValue_{\text{lt}}\left(A_{\text{t}} \rightarrow B_{\text{t}}\right) &\equiv 1-e^{-\left(1-p\left(A_{\text{t}} \rightarrow B_{\text{t}}\right)\right)} \\ &\equiv 1-e^{-(b/N)}\end{aligned} \tag{125}$$

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

2.2.15. Necessary and sufficient conditions

Definition 2.48 (**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

$$\begin{aligned} p\left(A_t \leftrightarrow B_t\right) &\equiv \frac{\sum_{t=1}^{N}\left(\left(A_t \vee \underline{B}_t\right) \wedge \left(\underline{A}_t \vee B_t\right)\right)}{N} \\ &\equiv p\left(a_t\right) + p\left(d_t\right) \\ &\equiv \frac{N \times \left(p\left(a_t\right) + p\left(d_t\right)\right)}{N} \\ &\equiv \frac{a+d}{N} \\ &\equiv +1 \end{aligned} \tag{126}$$

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

Definition 2.49 (**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

$$\begin{aligned} {\tilde{\chi}^2}_{\text{Calculated}}\left(A_t \leftrightarrow B_t \mid A\right) &\equiv \frac{\left(a-\left(a+b\right)\right)^2}{A} + \\ &\quad \frac{d-\left(\left(c+d\right)\right)^2}{\underline{A}} \\ &\equiv \frac{b^2}{A} + \frac{c^2}{\underline{A}} \end{aligned} \tag{127}$$

or equally as

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

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.

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

Definition 2.50 (The left-tailed p Value of a necessary and sufficient condition relationship).

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

$$\begin{aligned} pValue_{\text{lt}}\left(A_t \leftrightarrow B_t\right) &\equiv 1 - e^{-(1-p(A_t \leftrightarrow B_t))} \\ &\equiv 1 - e^{-((b+c)/N)} \end{aligned} \tag{129}$$

In this context, a low p-value indicates again a statistical significance. Table 11 may provide an overview of the theoretical distribution of a necessary and sufficient condition.

Table 11. Necessary and sufficient condition.

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

2.2.18. Either or conditions

Definition 2.51 (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

$$\begin{aligned} p\left(A_t \succ\!\prec B_t\right) &\equiv \frac{\sum_{t=1}^{N}\left(\left(A_t \wedge \underline{B}_t\right) \vee \left(\underline{A}_t \wedge B_t\right)\right)}{N} \\ &\equiv p\left(b_t\right) + p\left(c_t\right) \\ &\equiv \frac{N \times \left(p\left(b_t\right) + p\left(c_t\right)\right)}{N} \\ &\equiv \frac{b+c}{N} \\ &\equiv +1 \end{aligned} \tag{130}$$

It is $p\left(A_t \succ\!\prec B_t\right) \equiv 1 - p\left(A_t <\!\!> B_t\right)$ (see Table 12).

Table 12. Either A_t or B_t relationship.

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

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

Definition 2.52 (**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

$$\begin{aligned} \tilde{\chi}^2{}_{\text{Calculated}}\left(\left(A_t \succ\!\prec B_t\right) \mid A\right) &\equiv \frac{\left(b-(a+b)\right)^2}{A} + \\ &\quad \frac{c-\left((c+d)\right)^2}{\underline{A}} \\ &\equiv \frac{a^2}{A} + \frac{d^2}{\underline{A}} \end{aligned} \tag{131}$$

or equally as

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

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

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

Definition 2.53 (**The left-tailed p Value of an either or condition relationship**).

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

$$\begin{aligned} pValue_{\mathrm{lt}}\left(A_{\mathrm{t}} \succ\!\prec B_{\mathrm{t}}\right) &\equiv 1 - e^{-(1-p(A_{\mathrm{t}}>-<B_{\mathrm{t}}))} \\ &\equiv 1 - e^{-((a+d)/N)} \end{aligned} \tag{133}$$

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

2.2.21. Causal relationship k

The history of the denialism of causality in Philosophy, Mathematics, Statistics, Physics et cetera is very long. We only recall David Hume's (1711-1776) account of causation and his inappropriate reduction of the cause-effect relationship to a simple habitual connection in human thinking or Immanuel Kant's (1724-1804) initiated trial to consider causality as nothing more but a '*a priori*'given category (Langsam, 1994) in human reasoning and other similar attempts too. It is worth noting in this context that especially Karl Pearson (1857 - 1936) himself has been engaged in a long lasting and never-ending crusade against causation too. "**Pearson categorically denies the need for an independent concept of causal relation beyond correlation ... he *exterminated* causation from statistics before it had a chance to take root** "(Pearl, 2000) At the beginning of the 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 2.54 (**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

$$\begin{aligned} k\left(U_t, W_t\right) &\equiv \frac{\sigma\left(U_t, W_t\right)}{\sigma\left(U_t\right) \times \sigma\left(W_t\right)} \\ &\equiv \frac{p\left(U_t \wedge W_t\right) - p\left(U_t\right) \times p\left(W_t\right)}{\sqrt[2]{\left(p\left(U_t\right) \times \left(1 - p\left(U_t\right)\right)\right) \times \left(p\left(W_t\right) \times \left(1 - p\left(W_t\right)\right)\right)}} \end{aligned} \tag{134}$$

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

Table 13. 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.

2.2.22. Cause and effect

Definition 2.55 (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 14 may illustrate this relationship.

Table 14. 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

$$(U_t \vee \underline{W}_t) \equiv (\underline{W}_t \vee U_t) \equiv ((U_t \vee \underline{W}_t) \wedge (\underline{W}_t \vee U_t)) \equiv +1 \tag{135}$$

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

$$(\underline{U}_t \vee W_t) \equiv (W_t \vee \underline{U}_t) \equiv ((\underline{U}_t \vee W_t) \wedge (W_t \vee \underline{U}_t)) \equiv +1 \tag{136}$$

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

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

However, I think it necessary to make a clear distinction between a necessary and sufficient condition and the converse relationship (Eq. 135) above.

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

2.3. Axioms

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

2.3.1. Axiom I. Lex identitatis

In this context, we define axiom I as the expression

$$+1 = +1 \tag{139}$$

Backed by thousands of years of often bitter human experience, the scientific development has taught us all that human knowledge is relative too. Even if experiments and other suitable proofs are of help to encourage us more and more in our belief of the correctness of a theory, it is difficult to prove the correctness of a theorem or of a theory et cetera once and for all. Recall Einstein's position again: **"Niemals aber kann die Wahrheit einer Theorie erwiesen werden. Denn niemals weiß man, daß auch in Zukunft eine Erfahrung bekannt werden wird, die Ihren Folgerungen widerspricht..."** (Einstein, 1919). Albert Einstein's position translated into English: 'But the truth of a theory can never be proven. For one never knows if future experience will contradict its conclusion; and furthermore, there are always other conceptual systems imaginable which might coordinate the very same facts. '. Theories can be refuted.

> "No amount of experimentation can ever prove me right;
> **a single experiment can prove me wrong**."
>
> (Albert Einstein according to: Robertson, 1997)

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

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

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

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

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

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

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

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

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

2.3.2. Axiom II. Lex contradictionis

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

$$+0 = +1 \tag{140}$$

and equally the most simple form of a contradiction formulated.

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

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

2.3.3. Axiom III. Lex negationis

$$\neg(0) \times 0 = 1 \tag{141}$$

where $\neg$ denotes (logical (Boole, 1854) or natural) negation (Ayer, 1952, Förster and Melamed, 2012, Hedwig, 1980, Heinemann, Fritz H., 1943, Horn, 1989, Koch, 1999, Kunen, 1987, Newstadt, 2015, Royce, 1917, Speranza and Horn, 2010, Wedin, 1990b). In this context, there is some evidence that $\neg(1) \times 1 = 0$. In other words, it is $(\neg(1) \times 1) \times (\neg(0) \times 0) = 1$. Concepts like identity, difference, negation, opposition et cetera engaged the attention of scholars at least over the last twenty-three centuries (see also Horn, 1989, Speranza and Horn, 2010). As long as we first and foremost follow Josiah Royce, negatio or negation "is one of the simplest and most fundamental relations known to the human mind. For the study of logic, no more important and fruitful relation is known." (see also Royce, 1917, p. 265) But, do we really know what for sure, what negation is? Based on what we know about negation, Aristotle (see also Wedin, 1990a) has been one of the first to present a theory of negation, which can be found in discontinuous chunks in his works the Metaphysics, he Categories, De Interpretatione, and the Prior Analytics (see also Horn, 1989, p. 1). Negation (see also Newstadt, 2015) as a fundamental philosophical concept found its own very special melting point especially in Hegel's dialectic and is more than just a formal logical process or operation which converts only true to false and false to true. Negation as such is a natural process too and equally '**an engine of changes of objective reality** " (see also Barukčić, 2019a) . However, it remains an open question to establish a generally accepted link between this fundamental philosophical concept and an adequate counterpart in physics, mathematics and mathematical statistics et cetera. Especially the relationship between creatio ex nihilio (see also Donnelly, 1970, Ehrhardt, 1950, Ford, 1983) determination and negation (see also Ayer, 1952, Hedwig, 1980, Heinemann, Fritz H., 1943, Kunen, 1987) has been discussed in science since ancient (see also Horn, 1989, Speranza and Horn, 2010) times too. The development of the notion negation leads from Aristotle to Meister Eckhart von Hochheim, commonly known as Meister Eckhart (see also Tsopurashvili, 2012) or Eckehart, to Spinoza (1632 – 1677), to Immanuel Kant (1724-1804) and finally to Georg Wilhelm Friedrich Hegel (1770-1831) and other authors too. One point is worth being

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

3. Results

3.1. Herpes simplex virus-1 and schizoprenia

Theoretically, schizophrenia could by determined by prior exposure to neurotropic pathogens, or by a reactivation of the same. Lot D de Witte et al. [31] investigated in a case-control study (368 patients and 282 controls) the relationship between herpes simplex virus-1 (HSV-1) measured by pathogen-specific immunoglobulin G (IgG) in plasma and schizophrenia . Measuring pathogen-specific IgG is to some extent indicative of exposure to a certain pathogen. de Witte et al. were not able to find any significant differences in antibody titers of patients and controls for any of the six pathogens. de Witte et al. published data which are presented by table 15.

Table 15. HSV-1 IgG and Schizophrenia (Study de Witte et al. , 2015).

		Schizophrenia		
		YES	NO	
HSV-1 IgG	YES	133	120	253
	NO	235	162	397
		368	282	650

Statistical analysis.	
Causal relationship k =	-0.0651746667
p Value left tailed (HGD) =	0.0570907
p (SINE) =	0.6384615385
$\tilde{\chi}^2$ (SINE — B_t) =	150.0679
$\tilde{\chi}^2$ (SINE — $\underline{A}_t$) =	139.1058
p Value (SINE) =	0.3033961969
Additional measures.	
OR =	0.4538
IOR =	-0.0715
Study design.	
p(IOU)=	0.044615385
p(IOI)=	0.176923077

The data are partly self-contradictory. Nevertheless, a significant necessary condition relationship between herpes simplex virus-1 and schizoprenia is neither recognizable nor provable.

[31] de Witte LD, van Mierlo HC, Litjens M, Klein HC, Bahn S, Osterhaus AD; GROUP Investigators. The association between antibodies to neurotropic pathogens and schizophrenia: a case-control study. NPJ Schizophr. 2015 Nov 4;1:15041. doi: 10.1038/npjschz.2015.41. PMID: 27336045; PMCID: PMC4849462.

3.2. *Herpes simplex virus-2 and schizoprenia*

Theoretically, schizophrenia could by determined by prior exposure to neurotropic pathogens, or by a reactivation of the same. Lot D de Witte et al. [32] investigated in a case-control study (368 patients and 282 controls) the relationship between herpes simplex virus-2 (HSV-2) measured by pathogen-specific immunoglobulin G (IgG) in plasma and schizophrenia . Measuring pathogen-specific IgG is to some extent indicative of exposure to a certain pathogen. de Witte et al. were not able to find any significant differences in antibody titers of patients and controls for any of the six pathogens. de Witte et al. published data which are presented by table 16 .

Table 16. HSV-2 IgG and Schizophrenia (Study de Witte et al. , 2015).

		Schizophrenia		
		YES	NO	
HSV-2 IgG	YES	11	11	22
	NO	357	271	628
		368	282	650

Statistical analysis.	
Causal relationship k =	-0.0249833982
p Value left tailed (HGD) =	0.3356353
p (SINE) =	0.4507692308
$\tilde{\chi}^2$ (SINE — B_t) =	346.3288
$\tilde{\chi}^2$ (SINE — $\underline{A}_t$) =	202.9443
p Value (SINE) =	0.4226062113
Additional measures.	
OR =	0.4338
IOR =	-0.1168
Study design.	
p(IOU)=	0.4
p(IOI)=	0.532307692

Even these data are partly self-contradictory. Nevertheless, a significant necessary condition relationship between herpes simplex virus-2 and schizoprenia is neither recognizable nor provable.

[32] de Witte LD, van Mierlo HC, Litjens M, Klein HC, Bahn S, Osterhaus AD; GROUP Investigators. The association between antibodies to neurotropic pathogens and schizophrenia: a case-control study. NPJ Schizophr. 2015 Nov 4;1:15041. doi: 10.1038/npjschz.2015.41. PMID: 27336045; PMCID: PMC4849462.

3.3. *Epstein-Barr virus and schizoprenia*

Theoretically, schizophrenia could by determined by prior exposure to neurotropic pathogens, or by a reactivation of the same. Lot D de Witte et al. [33] investigated in a case-control study (368 patients and 282 controls) the relationship between Epstein-Barr virus (EBV) measured by pathogen-specific immunoglobulin G (IgG) in plasma and schizophrenia . Measuring pathogen-specific IgG is to some extent indicative of exposure to a certain pathogen. de Witte et al. were not able to find any significant differences in antibody titers of patients and controls for any of the six pathogens. de Witte et al. published data which are presented by table 17.

Table 17. EBV IgG and Schizophrenia (Study de Witte et al. , 2015).

		Schizophrenia		
		YES	NO	
EBV IgG	YES	264	208	472
	NO	104	74	178
		368	282	650

Statistical analysis.	
Causal relationship k =	-0.0224471813
p Value left tailed (HGD) =	0.3148709
p (SINE) =	0.8400000000
$\tilde{\chi}^2$ (SINE — B_t) =	29.3913
$\tilde{\chi}^2$ (SINE — $\underline{A}_t$) =	60.7640
p Value (SINE) =	0.1478562110
Additional measures.	
OR =	0.5200
IOR =	-0.0121
Study design.	
p(IOU)=	0.292307692
p(IOI)=	0.16

The data presented before are to some extent self-contradictory too. Nevertheless, a significant necessary condition relationship between Epstein-Barr virus and schizoprenia is neither recognizable nor provable.

[33] de Witte LD, van Mierlo HC, Litjens M, Klein HC, Bahn S, Osterhaus AD; GROUP Investigators. The association between antibodies to neurotropic pathogens and schizophrenia: a case-control study. NPJ Schizophr. 2015 Nov 4;1:15041. doi: 10.1038/npjschz.2015.41. PMID: 27336045; PMCID: PMC4849462.

3.4. Cytomegalovirus and schizoprenia

Theoretically, schizophrenia could by determined by prior exposure to neurotropic pathogens, or by a reactivation of the same. Lot D de Witte et al. [34] investigated in a case-control study (368 patients and 282 controls) the relationship between cytomegalovirus (CMV) measured by pathogen-specific immunoglobulin G (IgG) in plasma and schizophrenia. Measuring pathogen-specific IgG is to some extent indicative of exposure to a certain pathogen. de Witte et al. were not able to find any significant differences in antibody titers of patients and controls for any of the six pathogens. de Witte et al. published data which are presented by table 18.

Table 18. CMV IgG and Schizophrenia (Study de Witte et al. , 2015).

		Schizophrenia		
		YES	NO	
CMV IgG	YES	102	114	216
	NO	266	168	434
		368	282	650

Statistical analysis.	
Causal relationship k =	-0.1337084132
p Value left tailed (HGD) =	0.0004516
p (SINE) =	0.5907692308
$\tilde{\chi}^2$ (SINE — B_t) =	192.2717
$\tilde{\chi}^2$ (SINE — $\underline{A}_t$) =	163.0323
p Value (SINE) =	0.3358390533
Additional measures.	
OR =	0.4154
IOR =	-0.1659
Study design.	
p(IOU)=	0.101538462
p(IOI)=	0.233846154

The data presented before are to a lesser extent self-contradictory too. Nevertheless, a significant necessary condition relationship between cytomegalovirus and schizoprenia is neither recognizable nor provable.

[34] de Witte LD, van Mierlo HC, Litjens M, Klein HC, Bahn S, Osterhaus AD; GROUP Investigators. The association between antibodies to neurotropic pathogens and schizophrenia: a case-control study. NPJ Schizophr. 2015 Nov 4;1:15041. doi: 10.1038/npjschz.2015.41. PMID: 27336045; PMCID: PMC4849462.

3.5. *Toxoplasma gondii and schizoprenia*

Theoretically, schizophrenia could by determined by prior exposure to neurotropic pathogens, or by a reactivation of the same. Lot D de Witte et al. [35] investigated in a case-control study (368 patients and 282 controls) the relationship between Toxoplasma gondii (TG) measured by pathogen-specific immunoglobulin G (IgG) in plasma and schizophrenia . Measuring pathogen-specific IgG is to some extent indicative of exposure to a certain pathogen. de Witte et al. were not able to find any significant differences in antibody titers of patients and controls for any of the six pathogens. de Witte et al. published data which are presented by table 19 .

Table 19. TG IgG and Schizophrenia (Study de Witte et al. , 2015).

		Schizophrenia		
		YES	NO	
TG IgG	YES	68	50	118
	NO	300	232	532
		368	282	650

Statistical analysis.	
Causal relationship k =	0.0096142727
p Value left tailed (HGD) =	0.6349802
p (SINE) =	0.5384615385
$\tilde{\chi}^2$ (SINE — B_t) =	244.5652
$\tilde{\chi}^2$ (SINE — $\underline{A}_t$) =	169.1729
p Value (SINE) =	0.3696868134
Additional measures.	
OR =	0.4615
IOR =	0.0179
Study design.	
p(IOU)=	0.252307692
p(IOI)=	0.384615385

The data presented before are slightly biased. Hover, a significant necessary condition relationship between toxoplasma gondii and schizoprenia does not exist.

[35] de Witte LD, van Mierlo HC, Litjens M, Klein HC, Bahn S, Osterhaus AD; GROUP Investigators. The association between antibodies to neurotropic pathogens and schizophrenia: a case-control study. NPJ Schizophr. 2015 Nov 4;1:15041. doi: 10.1038/npjschz.2015.41. PMID: 27336045; PMCID: PMC4849462.

3.6. *Varicella zoster virus and schizoprenia*

Theoretically, schizophrenia could by determined by prior exposure to neurotropic pathogens, or by a reactivation of the same. Lot D de Witte et al. [36] investigated in a case-control study (368 patients and 282 controls) the relationship between varicella zoster virus (VZV) measured by pathogen-specific immunoglobulin G (IgG) in plasma and schizophrenia . Measuring pathogen-specific IgG is to some extent indicative of exposure to a certain pathogen. de Witte et al. were not able to find any significant differences in antibody titers of patients and controls for any of the six pathogens. de Witte et al. published data which are presented by table 20.

Table 20. VZV IgG and Schizophrenia (Study de Witte et al. , 2015).

		Schizophrenia		
		YES	NO	
VZV IgG	YES	352	279	631
	NO	16	3	19
		368	282	650

Statistical analysis.	
Causal relationship k =	-0.0966183558
p Value left tailed (HGD) =	0.0102536
p (SINE) =	0.9753846154
$\tilde{\chi}^2$ (SINE — B_t) =	0.6957
$\tilde{\chi}^2$ (SINE — $\underline{A}_t$) =	13.4737
p Value (SINE) =	0.0243148966
Additional measures.	
OR =	0.5462
IOR =	-0.0147
Study design.	
p(IOU)=	0.536923077
p(IOI)=	0.404615385

The data presented before are potentially biased. Hover, a significant necessary condition relationship between varicella zoster virus and schizoprenia does exist (p Value (SINE) = 0.0243148966). According to the data before, **without** varicella zoster virus infection / reactivation, **no** schizophrenia (p (SINE) = +0.9958847737; p Value (SINE) = 0.0041067704; however: $k < 0$!!!).

[36] de Witte LD, van Mierlo HC, Litjens M, Klein HC, Bahn S, Osterhaus AD; GROUP Investigators. The association between antibodies to neurotropic pathogens and schizophrenia: a case-control study. NPJ Schizophr. 2015 Nov 4;1:15041. doi: 10.1038/npjschz.2015.41. PMID: 27336045; PMCID: PMC4849462.

3.7. Varicella zoster virus and schizoprenia II

Theoretically, schizophrenia could by determined by prior exposure to neurotropic pathogens, or by a reactivation of the same. Lot D de Witte et al. [37] investigated in a case-control study (368 patients and 282 controls) the relationship between varicella zoster virus (VZV) measured by pathogen-specific immunoglobulin G (IgG) in plasma and schizophrenia. Measuring pathogen-specific IgG is to some extent indicative of exposure to a certain pathogen. de Witte et al. were not able to find any significant differences in antibody titers of patients and controls for any of the six pathogens. The prevalence of varicella zoster virus in the control group of the study of de Witte et al. is 100*(279/282)= 98.9361702 %, which is too high. [38] , [39] , [40] We constructed a fictive control group. The original data of de Witte et al. and the data of the fictive control group (in blue colour) are presented by table 21.

[37]de Witte LD, van Mierlo HC, Litjens M, Klein HC, Bahn S, Osterhaus AD; GROUP Investigators. The association between antibodies to neurotropic pathogens and schizophrenia: a case-control study. NPJ Schizophr. 2015 Nov 4;1:15041. doi: 10.1038/npjschz.2015.41. PMID: 27336045; PMCID: PMC4849462.

[38]Garnett GP, Grenfell BT. The epidemiology of varicella-zoster virus infections: the influence of varicella on the prevalence of herpes zoster. Epidemiol Infect. 1992 Jun;108(3):513-28. doi: 10.1017/s0950268800050019. PMID: 1318219; PMCID: PMC2272211.

[39]Gilden D, White T, Khmeleva N, Heintzman A, Choe A, Boyer PJ, Grose C, Carpenter JE, Rempel A, Bos N, Kandasamy B, Lear-Kaul K, Holmes DB, Bennett JL, Cohrs RJ, Mahalingam R, Mandava N, Eberhart CG, Bockelman B, Poppiti RJ, Tamhankar MA, Fogt F, Amato M, Wood E, Durairaj V, Rasmussen S, Petursdottir V, Pollak L, Mendlovic S, Chatelain D, Keyvani K, Brueck W, Nagel MA. Prevalence and distribution of VZV in temporal arteries of patients with giant cell arteritis. Neurology. 2015 May 12;84(19):1948-55. doi: 10.1212/WNL.0000000000001409. Epub 2015 Feb 18. PMID: 25695965; PMCID: PMC4433460.

[40]Liyanage NP, Fernando S, Malavige GN, Mallikahewa R, Sivayogan S, Jiffry MT, Vitarana T. Seroprevalence of varicella zoster virus infections in Colombo district, Sri Lanka. Indian J Med Sci. 2007 Mar;61(3):128-34. PMID: 17337813.

Table 21. VZV IgG and Schizophrenia (Study de Witte et al. , 2015 (fictitious control group)).

		Schizophrenia		
		YES	NO	
VZV IgG	YES	352	3168	3520
	NO	16	352	368
		368	3520	3888

Statistical analysis.	
Causal relationship k =	0.0565217391
p Value left tailed (HGD) =	0.9999626
p (SINE) =	0.9958847737
$\tilde{\chi}^2$ (SINE — B_t) =	0.6957
$\tilde{\chi}^2$ (SINE — $\underline{A}_t$) =	0.6957
p Value (SINE) =	0.0041067704
Additional measures.	
OR =	0.1811
IOR =	0.0565
Study design.	
p(IOU)=	0
p(IOI)=	0.810699588

Under conditions of fair study design (p(IOU)=0), the data of table 21 are based on the assumption that the prevalence of varicella zoster virus in the control group is about 90 %. We obtain 352 = 10 % or X = 3520. A matching 1:10 by de Witte et al. would have been more appropriate to detect the true relationship between VZV and schizophrenia. Under conditions of fa air study design and a prevalence in the control group which is closer to reality, the thought pushes itself with all possible might. **Without** varicella zoster virus infection / reactivation, **no** schizophrenia (p (SINE) = +0.9958847737; p Value (SINE) = 0.0041067704; $k > 0$). The logical conclusion is inevitable that the cause of schizophrenia can be found in a varicella zoster virus infection / reactivation.

3.8. Varicella zoster virus and schizophreniaia III

The following considerations are based on the assumption that the prevalence of varicella zoster virus of about 352/368 = 95.652173913 % as found by de Witte et al. in patients with schizophrenia is more or less correct. In order to work out the possible relationship between schizophrenia and varicella zoster virus very precisely, we construct the following, fictitious control group. The data of Vojgani et al. [41] are taken as the foundation of prevalence in the new fictitious control group. As a fictitious control group, we considered children up to the age of 7 months who were definitely free of schizophrenia. The prevalence of VZV in children up to 7 months of age is 4.6%. Under conditions of fair study design (p(IOU) = 0), it is 352 = 95.4 %. The sample size of the fictitious control group of children up to the age of 7 months which are free of schizophrenia follows as 369.

Table 22. VZV IgG and Shizophrenia (Study de Witte et al.,2015 (fictitious control group)).

		Shizophrenia		
		YES	NO	
VZV IgG	YES	352	17	369
	NO	16	352	368
		368	369	737

Statistical analysis.	
Causal relationship k =	0,9104512784
p Value right tailed (HGD) =	0,0000000000
p (SINE) =	0,9782903664
$\tilde{\chi}^2$ (SINE — B_t) =	0,6957
$\tilde{\chi}^2$ (SINE — $\underline{A}_t$) =	0,6957
p Value (SINE) =	0,0214756757
Additional measures.	
OR =	0,9552
IOR =	0,9105
Study design.	
p(IOU)=	0
p(IOI)=	0,001356852

4. Discussion

However, this study has some limitations. It is to be noted that 16 patients were VZV negative but were identified as suffering from with schizophrenia. This is not unproblematic and provides fundamental evidence against the possibility that VZV is a necessary condition of schizophrenia. Nonethe-

[41] Vojgani Y, Zarei S, Rajaei S, Chamani-Tabriz L, Ghaemimanesh F, Mohammadinia N, Jeddi-Tehrani M. Sero-Prevalence of Antibodies against Varicella Zoster Virus in Children under Seven-Years Old in 2012 in Tehran, Iran. Iran J Public Health. 2014 Nov;43(11):1569-75. PMID: 26060726; PMCID: PMC4449508.

less, the question arises, did these 16 patients really suffered from schizophrenia? The diagnosis of a schizophrenia by the study group has been done according to the Comprehensive Assessment of Symptoms and History (CASH) [42] or according to the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) [43] interview using the DSM-IV. However, these are none objective diagnostic methods for the diagnosis of schizophrenia. In other words, it cannot be ruled out completely that these 16 patients were classified as schizophrenic patients but did not suffer from schizophrenia. Furthermore, IgG antibodies against HSV-1, HSV-2, VZV, EBV, CMV, and TG were determined by a commercial enzyme-linked immunosorbent assay (ELISA) tests (IBL Laboratories, Hamburg, Germany). However, the ability of these methods to recognise VZV positive people as such is less than 100%. The sensitivity and specificity [44] of the methods used method has been about 95%. That is to say, for example, out of 400 VZV-positive people, about 20 individuals cannot be recognized as VZV-positive even if all 400 people are VZV-positive. At least for these reasons, we need a P Value as part of our decisions. The situation is further complicated by the study design of the study with p(IOU)= 0.536923077, which was not very convincing. Against the background of these individual comments, the question arises whether the data of the study of de Witte et al. [45] are of any value at all. However, despite all these difficulties, it is necessary to go on reiterating the point that the data of the study of de Witte et al. [46] do support the hypothesis **without** VZV infection **no** schizophrenia (P value = 0.0243148966). Further and more detailed investigations in this context are necessary. In general, more than 90% of adults have been infected with varicella zoster virus [47] and are at the end at risk for herpes zoster. On primary exposure, varicella zoster virus causes chickenpox (varicella). However, later in life, varicella zoster virus can reactivate [48] to cause shingles (herpes zoster) and other pathological changes. An effective vaccination [49] against varicella zoster virus should be able to prevent these processes including schizophrenia too. Shingrix is one vaccine [50] , [51] used for prevention of herpes zoster (HZ) and post-herpetic neuralgia (PHN) and able to induce antigen-specific cellular and humoral immune responses in individuals, Zostavax [52] (Merck), the live-attenuated vaccine against herpes zoster, is another one. The primary

[42] Andreasen NC, Flaum M, Arndt S. The Comprehensive Assessment of Symptoms and History (CASH). An instrument for assessing diagnosis and psychopathology. Arch Gen Psychiatry. 1992 Aug;49(8):615-23. doi: 10.1001/archpsyc.1992.01820080023004. PMID: 1637251.

[43] Wing JK, Babor T, Brugha T, Burke J, Cooper JE, Giel R, Jablenski A, Regier D, Sartorius N. SCAN. Schedules for Clinical Assessment in Neuropsychiatry. Arch Gen Psychiatry. 1990 Jun;47(6):589-93. doi: 10.1001/archpsyc.1990.01810180089012. PMID: 2190539.

[44] Ibid.

[45] de Witte LD, van Mierlo HC, Litjens M, Klein HC, Bahn S, Osterhaus AD; GROUP Investigators. The association between antibodies to neurotropic pathogens and schizophrenia: a case-control study. NPJ Schizophr. 2015 Nov 4;1:15041. doi: 10.1038/npjschz.2015.41. PMID: 27336045; PMCID: PMC4849462.

[46] Ibid.

[47] Johnson RW. Herpes zoster and postherpetic neuralgia. Expert Rev Vaccines. 2010 Mar;9(3 Suppl):21-6. doi: 10.1586/erv.10.30. PMID: 20192714.

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[49] Tricco AC, Zarin W, Cardoso R, Veroniki AA, Khan PA, Nincic V, Ghassemi M, Warren R, Sharpe JP, Page AV, Straus SE. Efficacy, effectiveness, and safety of herpes zoster vaccines in adults aged 50 and older: systematic review and network meta-analysis. BMJ. 2018 Oct 25;363:k4029. doi: 10.1136/bmj.k4029. PMID: 30361202; PMCID: PMC6201212.

[50] Lal H, Cunningham AL, Godeaux O, Chlibek R, Diez-Domingo J, Hwang SJ, Levin MJ, McElhaney JE, Poder A, Puig-Barberà J, Vesikari T, Watanabe D, Weckx L, Zahaf T, Heineman TC; ZOE-50 Study Group. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. N Engl J Med. 2015 May 28;372(22):2087-96. doi: 10.1056/NEJMoa1501184. Epub 2015 Apr 28. PMID: 25916341.

[51] ClinicalTrials.gov number, NCT01165177

[52] Schmader KE, Levin MJ, Gnann JW Jr, McNeil SA, Vesikari T, Betts RF, Keay S, Stek JE, Bundick ND, Su SC, Zhao Y, Li X, Chan IS, Annunziato PW, Parrino J. Efficacy, safety, and tolerability of herpes zoster vaccine in persons aged 50-59 years. Clin Infect

Shingrix vaccination schedule consists of two doses of 0.5 mL each: an initial dose followed by a second dose 2 months later. Furthermore, a treatment of patients with a highly acute schizophrenia by intravenous immune globulin (1 g per kilogram per day for 2-5 days) should be better than placebo and would provide additional evidence of the hypothesis **without** VZV infection **no** schizophrenia (P value = 0.0243148966).

5. Conclusion

Without VZV infection **no** schizophrenia (P value = 0.0243148966).

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6. Patient consent for publication

Not required.

Conflict of interest statement

No conflict of interest to declare.

Private note

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

This article has been pre-published and deposited at viXra [53] 2019-11-10 04:05:32.

Dis. 2012 Apr;54(7):922-8. doi: 10.1093/cid/cir970. Epub 2012 Jan 30. PMID: 22291101; PMCID: PMC4542655.

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I was born October, 1st 1961 in Novo Selo, Bosnia and Herzegovina, former Yogoslavia. I am of Croatian origin. From 1982-1989 C.E., I studied human medicine at the University of Hamburg, Germany. Meanwhile, I am working as a specialist of internal medicine. My basic field of research since my high school days at the Wirtschaftsgymnasium Bruchsal, Baden Württemberg, Germany is the mathematization of the relationship between a cause and an effect valid without any restriction under any circumstances including the conditions of classical logic, probability theory, quantum mechanics, special and general theory of relativity, human medicine et cetera. I endeavour to investigate positions of quantum mechanics, relativity theory, mathematics et cetera, only insofar as these positions put into question or endanger **the general validity of the principle of causality**.

[a] https://orcid.org/0000-0002-6988-2780
[b] https://cel.webofknowledge.com/InboundService.do?app=wos&product=CEL&Func=Frame&SrcApp=Publons&SrcAuth=Publons_CEL&locale=en-US&SID=F4r5Tsr3OcrmFbYrqiF&customersID=Publons_CEL&smartRedirect=yes&mode=FullRecord&IsProductCode=Yes&Init=Yes&action=retrieve&UT=WOS%3A000298855300006
[c] https://publons.com/researcher/3501739/ilija-barukcic/
[d] https://www.scopus.com/authid/detail.uri?authorId=37099674500
[e] https://www.scopus.com/authid/detail.uri?authorId=54974181600
[f] https://www.mendeley.com/search/?authorFullName=Ilija%20Baruk%C4%8Di%C4%87&page=1&query=Barukcic&sortBy=relevance
[g] https://www.researchgate.net/profile/Ilija-Barukcic-2
[h] https://zenodo.org/search?page=1&size=20&q=keywords:%22Baruk%C4%8Di%C4%87%22&sort=mostviewed
[i] https://zenodo.org/search?page=1&size=20&q=keywords:%22Baruk%C4%8Di%C4%87,%20Conference%22
[j] https://twitter.com/ilijabarukcic?lang=de
[k] https://twitter.com/Causation_Journ
[l] https://vixra.org/author/ilija_barukcic
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