CAUSATION
International Journal of Science

CAUSATION, 17(7): 5–89

DOI:10.5281/zenodo.6480889
Received: April 24, 2022
Accepted: April 24, 2022
Published: April 24, 2022
Deutsche Nationalbibliothek Frankfurt

Epstein-Barr virus is the cause of human breast cancer

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:

Epstein-Barr virus (EBV) has been widely proposed as a possible candidate virus for the viral etiology of human breast cancer, still the most common malignancy affecting females worldwide.

Methods:

Due to possible problems with PCR analyses (contamination), the lack of uniformity in the study design and insufficient mathematical/statistical methods used by the different authors, findings of several EBV (polymerase chain reaction (PCR)) studies contradict each other making it very difficult to determine the EBV etiology for breast cancer.

Results:

The present systematic review and meta-analysis of (case-control) studies has been performed with new statistical methods. To place our results in context, the relationship between EBV and human breast cancer appears to be cleared.

Conclusion:

Epstein-Barr virus is the cause of human breast cancer.

Keywords: Epstein-Barr virus; Breast cancer; Causal relationship k; Causality; Causation

1. Introduction

Breast cancer (BC) is the most common [1] cancer among women worldwide. Unfortunately, BC is a life-threatening [2] disease too which is imposing a significant burden on public health with estimated 5-year survival rates of about 80% in developed countries and far below 40% for developing countries [3] . The reasons for a woman being afflicted with this often deadly disease are even after years of research still largely in the dark. Internal risk factors [4] such as genetic variation, hormones, a family history of

[1]Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014 Jan-Feb;64(1):9-29. doi: 10.3322/caac.21208. Epub 2014 Jan 7. Erratum in: CA Cancer J Clin. 2014 Sep-Oct;64(5):364. PMID: 24399786.

[2]Parkin DM. The global health burden of infection-associated cancers in the year 2002. International journal of cancer Journal international du cancer. 2006;118(12):3030–3044. doi: 10.1002/ijc.21731.

[3]Coleman MP, Quaresma M, Berrino F, Lutz JM, De Angelis R, Capocaccia R, Baili P, Rachet B, Gatta G, Hakulinen T, Micheli A, Sant M, Weir HK, Elwood JM, Tsukuma H, Koifman S, E Silva GA, Francisci S, Santaquilani M, Verdecchia A, Storm HH, Young JL; CONCORD Working Group. Cancer survival in five continents: a worldwide population-based study (CONCORD). Lancet Oncol. 2008 Aug;9(8):730-56. doi: 10.1016/S1470-2045(08)70179-7. Epub 2008 Jul 17. PMID: 18639491.

[4]Moore DH, Moore DH 2nd, Moore CT. Breast carcinoma etiological factors. Adv Cancer Res. 1983;40:189-253. doi: 10.1016/s0065-230x(08)60681-8. PMID: 6362356.

early onset breast cancer et cetera and various external risk factors [5] like life style (alcohol consumption [6] , smoking [7] , inactivity and obesity [8] et cetera) and environmental factors including different infectious agents like Epstein-Barr virus (EBV), mouse mammary tumor virus (MMTV), bovine leukemia virus, human papillomavirus [9] (HPV) et cetera are assumed to play major roles during initiation, development, and progression of breast cancer. Especially after Labrecque et al. [10] detected EBV DNA by PCR in 19/91 cases of human breast carcinoma, EBV has been investigated as an aetiological agent of human breast cancer. However, the studies used different methodologies or techniques (ISH, IHC and PCR) and there are dissimilarities concerning the quality of the archival materials (paraffin-embedded tissues, fresh/frozen tissues et cetera) making it difficult to determine whether there is a relationship between EBV and BC at all. By time, the epistemological fog on the relationship between EBV and BC didn't disappear at all, but became denser. A publication claimed to have found that EBV is localized within BC infiltrating lymphocytes rather than within malignant breast cancer cells. [11] In other words, EBV is nothing more but a secondary invader of BC and contributes nothing causative to this disease. It is hardly surprising, therefore, that despite numerous systematic reviews and meta-analysis [12] , [13] , [14] , [15] , [16] , [17] published regarding the relationship between Epstein-Barr virus and human breast cancer, this issue still remained controversial. Breast cancer is a major cause of mortality and a worldwide public health dilemma. The extremely high disease burden of BC highlights the need to challenge global breast cancer research through a new approach in order to identify the cause of human breast cancer.

[5] Rojas K, Stuckey A. Breast Cancer Epidemiology and Risk Factors. Clin Obstet Gynecol. 2016 Dec;59(4):651-672. doi: 10.1097/GRF.0000000000000239. PMID: 27681694.

[6] Allen NE, Beral V, Casabonne D, Kan SW, Reeves GK, Brown A, Green J; Million Women Study Collaborators. Moderate alcohol intake and cancer incidence in women. J Natl Cancer Inst. 2009 Mar 4;101(5):296-305. doi: 10.1093/jnci/djn514. Epub 2009 Feb 24. PMID: 19244173.

[7] Kawai M, Malone KE, Tang MT, Li CI. Active smoking and the risk of estrogen receptor-positive and triple-negative breast cancer among women ages 20 to 44 years. Cancer. 2014 Apr 1;120(7):1026-34. doi: 10.1002/cncr.28402. Epub 2014 Feb 10. PMID: 24515648; PMCID: PMC4090108.

[8] Silvera SA, Jain M, Howe GR, Miller AB, Rohan TE. Energy balance and breast cancer risk: a prospective cohort study. Breast Cancer Res Treat. 2006 May;97(1):97-106. doi: 10.1007/s10549-005-9098-3. Epub 2005 Dec 1. PMID: 16319973.

[9] Bae JM, Kim EH. Human papillomavirus infection and risk of breast cancer: a meta-analysis of case-control studies. Infect Agent Cancer. 2016 Mar 14;11:14. doi: 10.1186/s13027-016-0058-9. PMID: 26981149; PMCID: PMC4791894.

[10] Labrecque LG, Barnes DM, Fentiman IS, Griffin BE. Epstein-Barr virus in epithelial cell tumors: a breast cancer study. Cancer Res. 1995 Jan 1;55(1):39-45. PMID: 7805038.

[11] Khan G, Philip PS, Al Ashari M, Houcinat Y, Daoud S. Localization of Epstein-Barr virus to infiltrating lymphocytes in breast carcinomas and not malignant cells. Exp Mol Pathol. 2011 Aug;91(1):466-70. doi: 10.1016/j.yexmp.2011.04.018. Epub 2011 May 6. PMID: 21600202.

[12] Jin Q, Su J, Yan D, Wu S. Epstein-Barr Virus Infection and Increased Sporadic Breast Carcinoma Risk: A Meta-Analysis. Med Princ Pract. 2020;29(2):195-200. doi: 10.1159/000502131. Epub 2019 Jul 17. PMID: 31311020; PMCID: PMC7098296.

[13] Farahmand M, Monavari SH, Shoja Z, Ghaffari H, Tavakoli M, Tavakoli A. Epstein-Barr virus and risk of breast cancer: a systematic review and meta-analysis. Future Oncol. 2019 Aug;15(24):2873-2885. doi: 10.2217/fon-2019-0232. Epub 2019 Jul 25. PMID: 31342783.

[14] Richardson AK, Currie MJ, Robinson BA, Morrin H, Phung Y, Pearson JF, Anderson TP, Potter JD, Walker LC. Cytomegalovirus and Epstein-Barr virus in breast cancer. PLoS One. 2015 Feb 27;10(2):e0118989. doi: 10.1371/journal.pone.0118989. PMID: 25723522; PMCID: PMC4344231.

[15] Huo Q, Zhang N, Yang Q. Epstein-Barr virus infection and sporadic breast cancer risk: a meta-analysis. PLoS One. 2012;7(2):e31656. doi: 10.1371/journal.pone.0031656. Epub 2012 Feb 21. PMID: 22363698; PMCID: PMC3283657.

[16] Alibek K, Kakpenova A, Mussabekova A, Sypabekova M, Karatayeva N. Role of viruses in the development of breast cancer. Infect Agent Cancer. 2013 Sep 2;8:32. doi: 10.1186/1750-9378-8-32. PMID: 24138789; PMCID: PMC3765990.

[17] Joshi D, Buehring GC. Are viruses associated with human breast cancer? Scrutinizing the molecular evidence. Breast Cancer Res Treat. 2012 Aug;135(1):1-15. doi: 10.1007/s10549-011-1921-4. Epub 2012 Jan 25. PMID: 22274134.

2. Material and methods

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

2.1. Material

2.1.1. Literature search

A literature search was conducted using the electronic database PubMed until April 23, 2022. The keywords used for this systematic review were “case control”and “ebv”and “igg ”and “breast cancer”. The bibliographies of available or accessible articles were also reviewed for additional relevant publications. Reporting followed in adherence to Preferred Reporting [18] 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	8
Screening:		
	Articles excluded I	2
Eligibility:		
	Articles eligible for analysis	6
	Articles excluded II	0
Inclusion:		
	Studies included (meta-analysis)	6

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.

[18] 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.

2.1.2. 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.

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

2.1.3. Study selection and characteristics

The literature search yielded 8 potentially eligible titles. The abstracts were reviewed, inappropriate articles were excluded and removed. At the end, 6 articles which met the inclusion criteria were eligible for meta-analyses.

2.1.4. Data extraction and assessment of study quality

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

2.1.5. IgG based studies

Epstein–Barr virus (EBV) immunoglobulin G (IgG) antibody levels are able to provide evidence of EBV positivity of a human being and can be used to prove the relationship between EBV and breast

cancer too. The following EBV-VCA and EBNA-1 IgG [19] , [20] , [21] , [22] , [23] , [24] , [25] , [26] based studies were considered for reanalysis.

Epstein–Barr virus

Epstein–Barr virus (EBV), a double-stranded deoxyribonucleic acid (DNA) [27] human γ-herpes virus 4 (HHV4) [28], with a 170-kb-large genome [29] which encodes for various proteins and non-coding RNAs has been discovered 1964 by Michael Anthony Epstein, Bert Geoffrey Achong and Yvonne M. Barr [30]. After a generally asymptomatic primary EBV infection of mainly B-cells and epithelial cells usually during childhood, EBV resides latently [31] in resting B [32] cells for a lifetime. [33] However, under normal circumstances, an EBV infection is controlled by human immune system and individuals carrying EBV do not suffer from the viral infection. At the end, up to 95% of the adult population worldwide are infected by EBV at some time during their life span while the EBV seroprevalence increases with age

[19]Mashaly M, Ghorab D, Hegazy M, Abdelkhalek M, Gaballah K, Elzehery R. Association between Epstein-Barr Virus Gene Polymorphism and Breast Cancer Risk among Egyptian Females. Asian Pac J Cancer Prev. 2022 Feb 1;23(2):641-650. doi: 10.31557/APJCP.2022.23.2.641. PMID: 35225477.

[20]Richardson AK, Currie MJ, Robinson BA, Morrin H, Phung Y, Pearson JF, Anderson TP, Potter JD, Walker LC. Cytomegalovirus and Epstein-Barr virus in breast cancer. PLoS One. 2015 Feb 27;10(2):e0118989. doi: 10.1371/journal.pone.0118989. PMID: 25723522; PMCID: PMC4344231.

[21]Agborsangaya CB, Lehtinen T, Toriola AT, Pukkala E, Surcel HM, Tedeschi R, Lehtinen M. Association between Epstein-Barr virus infection and risk for development of pregnancy-associated breast cancer: joint effect with vitamin D? Eur J Cancer. 2011 Jan;47(1):116-20. doi: 10.1016/j.ejca.2010.07.006. Epub 2010 Aug 4. PMID: 20691583.

[22]He JR, Tang LY, Yu DD, Su FX, Song EW, Lin Y, Wang SM, Lai GC, Chen WQ, Ren ZF. Epstein-Barr virus and breast cancer: serological study in a high-incidence area of nasopharyngeal carcinoma. Cancer Lett. 2011 Oct 28;309(2):128-36. doi: 10.1016/j.canlet.2011.05.012. Epub 2011 Jun 24. PMID: 21724319.

[23]Cox B, Richardson A, Graham P, Gislefoss RE, Jellum E, Rollag H. Breast cancer, cytomegalovirus and Epstein-Barr virus: a nested case-control study. Br J Cancer. 2010 May 25;102(11):1665-9. doi: 10.1038/sj.bjc.6605675. Epub 2010 Apr 20. PMID: 20407437; PMCID: PMC2883146.

[24]Joshi D, Quadri M, Gangane N, Joshi R, Gangane N. Association of Epstein Barr virus infection (EBV) with breast cancer in rural Indian women. PLoS One. 2009 Dec 4;4(12):e8180. doi: 10.1371/journal.pone.0008180. PMID: 19997605; PMCID: PMC2782138.

[25]Richardson AK, Cox B, McCredie MR, Dite GS, Chang JH, Gertig DM, Southey MC, Giles GG, Hopper JL. Cytomegalovirus, Epstein-Barr virus and risk of breast cancer before age 40 years: a case-control study. Br J Cancer. 2004 Jun 1;90(11):2149-52. doi: 10.1038/sj.bjc.6601822. PMID: 15150559; PMCID: PMC2409506.

[26]case control and ebv and igg and breast cancer

[27]James Dewey Watson, Francis Harry Compton Crick. Molecular structure of nucleic acids; a structure for deoxyribose nucleic acid. Nature. 1953 Apr 25;171(4356):737-8. doi: 10.1038/171737a0. PMID: 13054692.

[28]Walker PJ, Siddell SG, Lefkowitz EJ, Mushegian AR, Adriaenssens EM, Alfenas-Zerbini P, Davison AJ, Dempsey DM, Dutilh BE, García ML, Harrach B, Harrison RL, Hendrickson RC, Junglen S, Knowles NJ, Krupovic M, Kuhn JH, Lambert AJ, Łobocka M, Nibert ML, Oksanen HM, Orton RJ, Robertson DL, Rubino L, Sabanadzovic S, Simmonds P, Smith DB, Suzuki N, Van Dooerslaer K, Vandamme AM, Varsani A, Zerbini FM. Changes to virus taxonomy and to the International Code of Virus Classification and Nomenclature ratified by the International Committee on Taxonomy of Viruses (2021). Arch Virol. 2021 Sep;166(9):2633-2648. doi: 10.1007/s00705-021-05156-1. PMID: 34231026.

[29]Feederle R, Klinke O, Kutikhin A, Poirey R, Tsai MH, Delecluse HJ. Epstein-Barr Virus: From the Detection of Sequence Polymorphisms to the Recognition of Viral Types. Curr Top Microbiol Immunol. 2015;390(Pt 1):119-48. doi: 10.1007/978-3-319-228228_7. PMID: 26424646.

[30]Michael Anthony Epstein, Bert Geoffrey Achong, Yvonne M. Barr. Virus Particles in Cultured Lymphoblasts from Burkitt's Lymphoma. Lancet. 1964 Mar 28;1(7335):702-3. doi: 10.1016/s0140-6736(64)91524-7. PMID: 14107961.

[31]Babcock GJ, Decker LL, Volk M, Thorley-Lawson DA. EBV persistence in memory B cells in vivo. Immunity. 1998 Sep;9(3):395-404. doi: 10.1016/s1074-7613(00)80622-6. PMID: 9768759.

[32]Miyashita EM, Yang B, Babcock GJ, Thorley-Lawson DA. Identification of the site of Epstein-Barr virus persistence in vivo as a resting B cell. J Virol. 1997 Jul;71(7):4882-91. doi: 10.1128/JVI.71.7.4882-4891.1997. Erratum in: J Virol 1998 Nov;72(11):9419. PMID: 9188550; PMCID: PMC191718.

[33]Amon W, Farrell PJ. Reactivation of Epstein-Barr virus from latency. Rev Med Virol. 2005 May-Jun;15(3):149-56. doi: 10.1002/rmv.456. PMID: 15546128.

(see table 2 [34]). “

Table 2. EBV seroprevalence increases with age.

Age y=year	EBV VCA IgG Pos no. (%)	EBV EBNA1 IgG Pos no. (%)	EBV VCA IgM Pos no. (%)	EBV VCA IgA Pos no. (%)	EB EA/D IgA Pos no. (%)
0–5y	283(66.59)	141(58.51)	65(14.57)	52(14.57)	26(7.12)
6–10y	431(84.34)	226(78.75)	55(10.24)	93(22.79)	39(9.18)
11–20y	784(92.89)	413(86.95)	123(10.41)	178(23.73)	95(12.20)
21–30y	809(98.54)	271(95.43)	88(6.25)	192(26.10)	120(15.33)
31–40y	853(98.84)	203(94.86)	40(3.06)	219(22.71)	123(11.80)
41–50y	892(99.78)	202(97.57)	36(2.76)	282(22.54)	171(13.13)
51–60y	957(99.79)	248(96.12)	37(2.62)	301(27.54)	184(15.79)
61–101y	902(99.01)	258(93.82)	29(2.03)	258(33.42)	146(18.36)

”. Meanwhile, various methods for the diagnosis of an Epstein-Barr virus (EBV) infection are available. In fact, it is necessary to differentiate [35] , [36] , [37] between a primary EBV infection and an EBV reactivation. Serological tests for immunoglobulin G (IgG)- and immunoglobulin M (IgM)-antibodies to Epstein-Barr virus viral capsid antigen (VCA) and IgG-antibodies to Epstein-Barr nuclear antigen 1 (EBNA-1) are frequently used to define infection status and for the differential diagnosis too. The presence of EBV VCA IgG and EBV VCA IgM without EBV EBNA-1 IgG indicates more or less an acute EBV infection, whereas the presence of VCA IgG and EBNA-1 IgG without VCA IgM is typical of past EBV infection [38]. However, immunoglobulin G (IgG) is representing approximately 75% of serum antibodies in humans and is is subject to very specific pharmacokinetics [39] and clearance. The plasma half-life [40] of IgG [41] , [42] , [43] is about 21 day. The human immune system does not always posses a reason or a possibility to produce EBV IgG or IgM antibodies. Especially, if there is no EBV re/infection, IgG is reduced by half about every 21 days and used for other purposes. Thus far, false positive and false negative IgG based results are theoretically possible. Furthermore, the sensitivity

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

[35] Robertson P, Beynon S, Whybin R, Brennan C, Vollmer-Conna U, Hickie I, Lloyd A. Measurement of EBV-IgG anti-VCA avidity aids the early and reliable diagnosis of primary EBV infection. J Med Virol. 2003 Aug;70(4):617-23. doi: 10.1002/jmv.10439. PMID: 12794726.

[36] De Paschale M, Clerici P. Serological diagnosis of Epstein-Barr virus infection: Problems and solutions. World J Virol. 2012 Feb 12;1(1):31-43. doi: 10.5501/wjv.v1.i1.31. PMID: 24175209; PMCID: PMC3782265.

[37] De Paschale M, Agrappi C, Manco MT, Mirri P, Viganò EF, Clerici P. Seroepidemiology of EBV and interpretation of the ”isolated VCA IgG” pattern. J Med Virol. 2009 Feb;81(2):325-31. doi: 10.1002/jmv.21373. PMID: 19107979.

[38] De Paschale M, Clerici P. Serological diagnosis of Epstein-Barr virus infection: Problems and solutions. World J Virol. 2012 Feb 12;1(1):31-43. doi: 10.5501/wjv.v1.i1.31. PMID: 24175209; PMCID: PMC3782265.

[39] WALDMANN TA, SCHWAB PJ. IGG (7 S GAMMA GLOBULIN) METABOLISM IN HYPOGAMMAGLOBULINEMIA: STUDIES IN PATIENTS WITH DEFECTIVE GAMMA GLOBULIN SYNTHESIS, GASTROINTESTINAL PROTEIN LOSS, OR BOTH. J Clin Invest. 1965 Sep;44(9):1523-33. doi: 10.1172/JCI105259. PMID: 14332165; PMCID: PMC292634.

[40] GORDON EB, WIENER AS. Studies on human serum gamma globulin. I. Half-life and rate of production. J Lab Clin Med. 1957 Feb;49(2):258-62. PMID: 13398691.

[41] Morell A, Terry WD, Waldmann TA. Metabolic properties of IgG subclasses in man. J Clin Invest. 1970 Apr;49(4):673-80. doi: 10.1172/JCI106279. PMID: 5443170; PMCID: PMC322522.

[42] Mankarious S, Lee M, Fischer S, Pyun KH, Ochs HD, Oxelius VA, Wedgwood RJ. The half-lives of IgG subclasses and specific antibodies in patients with primary immunodeficiency who are receiving intravenously administered immunoglobulin. J Lab Clin Med. 1988 Nov;112(5):634-40. PMID: 3183495.

[43] Bonilla FA. Pharmacokinetics of immunoglobulin administered via intravenous or subcutaneous routes. Immunol Allergy Clin North Am. 2008 Nov;28(4):803-19, ix. doi: 10.1016/j.iac.2008.06.006. PMID: 18940575.

and the specificity of EBV tests is not always equal to 100 %. EBV is discussed as the etiologic agent of infectious mononucleosis (Pfeiffersches Drüsenfieber, Morbus Pfeiffer), [44] , [45] , EBV DNA was detected in tissues from patients with nasopharyngeal carcinoma [46] , [47] , [48] and other tissues too. EBV is the cause of multiple sclerosis [49] , [50] , [51] , [52] , [53] , [54] , of rheumatoid arthritis [55] et cetera. Among other, high dose intravenous(i.v.) [56] , [57] L-ascorbic acid (vitamin C) [58] , [59] , [60] , [61] , [62] , valacyclovir

[44] Graser F. Hundert Jahre Pfeiffersches Drüsenfieber [100 years of Pfeiffer's glandular fever, Article in German]. Klin Padiatr. 1991 May-Jun;203(3):187-90. German. doi: 10.1055/s-2007-1025428. PMID: 1857056.

[45] Henle G, Henle W, Diehl V. Relation of Burkitt's tumor-associated herpes-ytpe virus to infectious mononucleosis. Proc Natl Acad Sci U S A. 1968 Jan;59(1):94-101. doi: 10.1073/pnas.59.1.94. PMID: 5242134; PMCID: PMC286007.

[46] zur Hausen H, Schulte-Holthausen H, Klein G, Henle W, Henle G, Clifford P, Santesson L. EBV DNA in biopsies of Burkitt tumours and anaplastic carcinomas of the nasopharynx. Nature. 1970 Dec 12;228(5276):1056-8. doi: 10.1038/2281056a0. PMID: 4320657.

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

[48] Barukčić, Ilija. (2022). Without Epstein–Barr virus infection, no nasopharyngeal carcinoma. Causation, 17(4), 5–65. https://doi.org/10.5281/zenodo.6386619

[49] Nikoskelainen J, Panelius M, Salmi A. E.B. virus and multiple sclerosis. Br Med J. 1972 Oct 14;4(5832):111. doi: 10.1136/bmj.4.5832.111. PMID: 4342670; PMCID: PMC1786242.

[50] Barukčić, K. and Barukčić, I. (2016) Epstein Barr Virus—The Cause of Multiple Sclerosis. Journal of Applied Mathematics and Physics, 4, 1042-1053. doi: 10.4236/jamp.2016.46109.

[51] Barukčić, Ilija. (2018). Epstein-Barr virus is the cause of multiple sclerosis. INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND PHARMACEUTICAL RESEARCH. Volume 4; Issue 9(A); September 2018; Page No. 3674-3682 https://doi.org/10.5281/zenodo.3943315

[52] Bjornevik K, Cortese M, Healy BC, Kuhle J, Mina MJ, Leng Y, Elledge SJ, Niebuhr DW, Scher AI, Munger KL, Ascherio A. Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis. Science. 2022 Jan 21;375(6578):296-301. doi: 10.1126/science.abj8222. Epub 2022 Jan 13. PMID: 35025605.

[53] Bjornevik K, Cortese M, Healy BC, Kuhle J, Mina MJ, Leng Y, Elledge SJ, Niebuhr DW, Scher AI, Munger KL, Ascherio A. Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis. Science. 2022 Jan 21;375(6578):296-301. doi: 10.1126/science.abj8222. Epub 2022 Jan 13. PMID: 35025605.

[54] Ludvig M. Sollid, Epstein-Barr virus as a driver of multiple sclerosis, Science Immunology, 7, 70, (2022). /doi/10.1126/sciimmunol.abo7799

[55] Katarina Barukčić, Jan Pavo Barukčić, Ilija Barukčić. Epstein-Barr virus is the cause of rheumatoid arthritis. ROMANIAN JOURNAL OF RHEUMATOLOGY – VOLUME 27, NO. 4, 2018. 148-163.

[56] Riordan HD, Hunninghake RB, Riordan NH, Jackson JJ, Meng X, Taylor P, Casciari JJ, González MJ, Miranda-Massari JR, Mora EM, Rosario N, Rivera A. Intravenous ascorbic acid: protocol for its application and use. P R Health Sci J. 2003 Sep;22(3):287-90. PMID: 14619456.

[57] Shatzer AN, Espey MG, Chavez M, Tu H, Levine M, Cohen JI. Ascorbic acid kills Epstein-Barr virus positive Burkitt lymphoma cells and Epstein-Barr virus transformed B-cells in vitro, but not in vivo. Leuk Lymphoma. 2013 May;54(5):1069-78. doi: 10.3109/10428194.2012.739686. Epub 2012 Nov 15. PMID: 23067008; PMCID: PMC4055524.

[58] Lind, James (1716-1794). A treatise of the scurvy, in three parts. Containing an inquiry into the nature, causes, and cure, of that disease. Together with a critical and chronological view of what has been published on the subject. Edinburgh (Scotland) : Printed by Sands, Murray and Cochran, for A. Kincaid & A. Donsaldson. 1753. 456 pages.

[59] Svirbely JL, Szent-Györgyi A. The chemical nature of vitamin C. Biochem J. 1932;26(3):865-70. doi: 10.1042/bj0260865. PMID: 16744896; PMCID: PMC1260981.

[60] Svirbely JL, Szent-Györgyi A. The chemical nature of vitamin C. Biochem J. 1933;27(1):279-85. PMID: 16745082; PMCID: PMC1252872.

[61] Linus Pauling. THE NATURE OF THE CHEMICAL BOND. APPLICATION OF RESULTS OBTAINED FROM THE QUANTUM MECHANICS AND FROM A THEORY OF PARAMAGNETIC SUSCEPTIBILITY TO THE STRUCTURE OF MOLECULES. Journal of the American Chemical Society 1931, 53, 4, 1367-1400.

[62] King CG, Waugh WA. THE CHEMICAL NATURE OF VITAMIN C. Science. 1932 Apr 1;75(1944):357-8. doi: 10.1126/science.75.1944.357-a. PMID: 17750032.

[63] , [64] or prednisolon [65] , [66] have been used to treat EBV. It has been reported that anti-EBNA1 EBV antibody levels decreased [67] , [68] by a supplementation with high-dose oral 25-hydroxyvitamin D3 (25(OH)D3). Regrettably, despite the massive EBV caused damage to individual [69] human beings and the hole human society, there is no antiviral drug approved for the treatment of (chronic active) EBV infections. [70]

2.1.6. Study design and bias

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

2.1.6.1. Index of unfairness (IOU)

Definition 2.1 (Index of unfairness).

[63] Lerner AM, Beqaj SH, Deeter RG, Dworkin HJ, Zervos M, Chang CH, Fitzgerald JT, Goldstein J, O'Neill W. A six-month trial of valacyclovir in the Epstein-Barr virus subset of chronic fatigue syndrome: improvement in left ventricular function. Drugs Today (Barc). 2002 Aug;38(8):549-61. doi: 10.1358/dot.2002.38.8.820095. PMID: 12582420.

[64] Lerner AM, Beqaj SH, Deeter RG, Fitzgerald JT. Valacyclovir treatment in Epstein-Barr virus subset chronic fatigue syndrome: thirty-six months follow-up. In Vivo. 2007 Sep-Oct;21(5):707-13. PMID: 18019402.

[65] Sawada A, Inoue M, Kawa K. How we treat chronic active Epstein-Barr virus infection. Int J Hematol. 2017 Apr;105(4):406-418. doi: 10.1007/s12185-017-2192-6. Epub 2017 Feb 16. PMID: 28210942.

[66] Tynell E, Aurelius E, Brandell A, Julander I, Wood M, Yao QY, Rickinson A, Akerlund B, Andersson J. Acyclovir and prednisolone treatment of acute infectious mononucleosis: a multicenter, double-blind, placebo-controlled study. J Infect Dis. 1996 Aug;174(2):324-31. doi: 10.1093/infdis/174.2.324. PMID: 8699062.

[67] Røsjø E, Lossius A, Abdelmagid N, Lindstrøm JC, Kampman MT, Jørgensen L, Sundström P, Olsson T, Steffensen LH, Torkildsen Ø, Holmøy T. Effect of high-dose vitamin D3 supplementation on antibody responses against Epstein-Barr virus in relapsing-remitting multiple sclerosis. Mult Scler. 2017 Mar;23(3):395-402. doi: 10.1177/1352458516654310. Epub 2016 Jul 11. PMID: 27325604.

[68] Najafipoor A, Roghanian R, Zarkesh-Esfahani SH, Bouzari M, Etemadifar M. The beneficial effects of vitamin D3 on reducing antibody titers against Epstein-Barr virus in multiple sclerosis patients. Cell Immunol. 2015 Mar;294(1):9-12. doi: 10.1016/j.cellimm.2015.01.009. Epub 2015 Jan 28. PMID: 25666504.

[69] Biebl A, Webersinke C, Traxler B, Povysil B, Furthner D, Schmitt K, Weis S. Fatal Epstein-Barr virus encephalitis in a 12-year-old child: an underappreciated neurological complication? Nat Clin Pract Neurol. 2009 Mar;5(3):171-4. doi: 10.1038/ncpneuro1043. PMID: 19262593.

[70] Andrei G, Trompet E, Snoeck R. Novel Therapeutics for EpsteinBarr Virus. Molecules. 2019 Mar 12;24(5):997. doi: 10.3390/molecules24050997. PMID: 30871092; PMCID: PMC6429425.

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

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

Under ideal conditions, it is desirable that an appropriate study design is able to assure as much as possible an index of unfairness (see Barukčić, 2019c) of p(IOU) = 0. In point of fact, against the background of lacking enough experience with the use of p(IOU), a p(IOU) up to 0.25 could be of use too. Especially under conditions where **a necessary condition relationship or a sufficient condition relationship** is tested, an index of unfairness is of use to prove whether sample data obtained are biased and to what extent. **without**

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

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

2.1.6.2. Index of independence (IOI)

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

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

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

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

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

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

Under ideal conditions, a study design which aims to prove **an exclusion relationship or a causal relationship** should assure as much as possible a p(IOI) = 0. However, once again, against the background of lacking enough experience with the use of p(IOI), sample data with a p(IOI) up to 0.25 are of

use too. Today, most double-blind placebo-controlled studies are based on the demand that **p(IOU) = p(IOI)** while the value of p(IOU) of has been widely neglected. Such an approach leads to unnecessary big sample sizes, the increase of cost, the waste of time and, most importantly of all, to epistemological systematically biased sample data and conclusions drawn. A change appears to be necessary.

2.1.7. 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. Additionally, the P Value has been calculated approximately (see also Barukčić, 2019d). The causal relationship k (Barukčić, 2016b, 2020a, 2021c) has been calculated to evaluate a possible causal relationship between the events. The hyper-geometric (Fisher, 1922, Gonin, 1936, Huygens and van Schooten, 1657, Pearson, 1899) distribution (HGD) has been used to test the one-sided significance of the causal relationship k. Bringing different studies together for analysing them or doing a meta-analysis is not without problems. Due to several reasons, there is variability in the data of the studies and there will be differences found. Usually, the heterogeneity among the studies is assessed through I^2 statistics [71] , [72] , [73] . Under usual circumstances, an I^2 value of 25%, 50% and 75% are regarded as low, moderate and high heterogeneity[74]. In this publication, the study (design) bias and the heterogeneity among the studies has been controlled by IOI, the index of independence (Barukčić, 2019b) and IOU, the index of unfairness (Barukčić, 2019c). All the data were analysed using MS Excel (Microsoft Corporation, USA). Under fair circumstances, P values less than 0.05 were considered statistically significant.

2.2. Methods

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

2.2.1. Random variables

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

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

[72] 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.

[73] 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.

[74] 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.

2.2.1.1. The Expectation of a Random Variable

Definition 2.3 (The First Moment Expectation of a Random Variable). *Summaries of an entire distribution of a random variable (see Kolmogorov, Andreĭ Nikolaevich, 1950, p. 22) X, such as the expected value, or average value, are useful in order to identify where X is expected to be without describing the entire distribution. For practical and other reasons, we shall limit ourselves here to discrete random variables, while the basic properties of the expectation value of a random variable X will not be investigated. Thus far, let X be a discrete random variable with the probability p(X). The relationship between the first moment expectation value (see Huygens and van Schooten, 1657, Kolmogorov, Andreĭ Nikolaevich, 1950, LaPlace, 1812, Whitworth, 1901) of X, denoted by E(X), and the probability p(X), is given by the equation:*

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

where $\Psi(X)$ is the wave-function (see Born, 1926, Schrödinger, Erwin Rudolf Josef Alexander, 1926) of X, $\Psi^{*}(X)$ is the complex conjugate wave-function of X. Under conditions where $p(X) \equiv +1$ equation 3 (see p. 16) becomes

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

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

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

The ongoing progress with artificial intelligence has the potential to transform human society far beyond any imaginable border of human recognition and can help even to solve problems that otherwise would not be tractable. No wonder, scientist and systems are confronted with large volumes of data (big data) of various natures and from different sources. The use of tensor technology can simplify and accelerate Big data analysis. In other words, let $X_{kl\mu\nu\ldots}$ denote an n-th index co-variant tensor with the probability $p(X_{kl\mu\nu\ldots})$. The first moment expectation value (see Huygens and van Schooten, 1657, Kolmogorov, Andreĭ Nikolaevich, 1950, LaPlace, 1812, Whitworth, 1901) of $X_{kl\mu\nu\ldots}$, denoted by $E(X_{kl\mu\nu\ldots})$, is a number defined as follows:

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

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

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

Definition 2.4 (**The Second Moment Expectation of a Random Variable**). *The second (see Kolmogorov, Andreĭ Nikolaevich, 1950, p. 42) moment expectation value (or more or less arithmetic mean) of a (large) number of independent realizations of a random variable X follows as:*

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

From the point of view of tensor algebra it is

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

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

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

2.2.1.2. Probability of a Random Variable What is the nature of the probability of an event, or what is the relationship between probability and geometry or between the probability of an event and notions like false or true. At a first pass, various authors answer this question, one way or another. For authors like De Morgan, probability is only a degree of confidence, or credences or of belief. "By degree of probability, we really mean, or ought to mean, degree of belief" (see De Morgan, 1847, p. 172). Such a purely subjective (or personalist or Bayesian (see Bayes, 1763)) interpretation of probabilities as degrees of confidence, or credences finds its own scientific opposition, moreover, in Kolmogorov's axiomatization of probability theory. However, perhaps we can do better, then, to think that Kolmogorov's axiomatization of probability theory is the last word spoken on probability theory. Nobody seriously considers that Kolmogorov's conceptual apparatus of probability theory has solved the basic problem of any probability theory, the relationship between classical logic or geometry and probability theory. One very massive disadvantage of Kolmogorov's axiomatization of probability theory is that it is very silent especially on this issue. Any unification of geometry and probability

theory into one unique mathematical framework might prove very difficult as long as we rely purely on Kolmogorov's understanding of probability theory. It's not surprising that the probability of an event bear at least directly, and sometimes indirectly, upon central philosophical and scientific concerns. A correct understanding of probability is one of the most important foundational scientific problems. Now let us strengthen our position with respect to the probability of an event. In our understanding, the probability of an event is something objectively and real. The probability of an event is the truth value of something or the degree to which something, i.e. a random variable X, is determined by its own expectation value. The probability p(X) of a random variable X follows as (see equation 3)

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

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

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

2.2.1.3. Variance of a Random Variable

Definition 2.6 (The Variance of a Random Variable). *Johann Carl Friedrich Gauß (1777-1855) introduced the normal distribution and the error of mean squared in his 1809 monograph (see Gauß, Carl Friedrich, 1809). In the following, Karl Pearson (1857-1936) coined the term "standard deviation"in 1893. Pearson is writing: "Then σ will be termed its standard-deviation (error of mean square)." (see Pearson, 1894, p. 80). Finally, the term variance was introduced by Sir Ronald Aylmer Fisher (1890-1962) in the year 1918.*

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

The deviation of a random variable X from its population mean or sample mean E(X) has a central role in statistics and is one important measure of dispersion. The variance $\sigma(X)^2$ (see Kolmogorov, Andreĭ Nikolaevich, 1950, p. 42), the second central moment of a distribution, is the expectation value of the squared deviation of a random variable X from its own expectation value E(X) and is determined in general as (see equation 8):

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

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

$$\begin{aligned}{}^2\sigma\left(X_{kl\mu\nu\ldots}\right) &\equiv E\left({}^2X_{kl\mu\nu\ldots}\right) - {}^2E\left(X_{kl\mu\nu\ldots}\right) \\ &\equiv \left(X_{kl\mu\nu\ldots} \times E\left(X_{kl\mu\nu\ldots}\right)\right) - {}^2E\left(X_{kl\mu\nu\ldots}\right) \\ &\equiv E\left(X_{kl\mu\nu\ldots}\right) \times \left(X_{kl\mu\nu\ldots} - E\left(X_{kl\mu\nu\ldots}\right)\right) \\ &\equiv E\left(X_{kl\mu\nu\ldots}\right) \times E\left(\underline{X}_{kl\mu\nu\ldots}\right)\end{aligned} \tag{14}$$

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 14, 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 [75] 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 13, it is

$$E\left(X^2\right) \equiv E(X)^2 + \sigma(X)^2 \tag{15}$$

or

$$\frac{E(X)^2}{E(X^2)} + \frac{\sigma(X)^2}{E(X^2)} \equiv p(X) + \frac{\sigma(X)^2}{E(X^2)} \equiv +1 \tag{16}$$

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

$$\begin{aligned}
\Psi(X) &\equiv \frac{1}{\Psi^*(X)} - \frac{\sigma(X)^2}{(\Psi^*(X) \times E(X^2))} \\
&\equiv \frac{\left(E\left(X^2\right) - \sigma(X)^2\right)}{(\Psi^*(X) \times E(X^2))} \\
&\equiv \frac{1}{(\Psi^*(X) \times E(X^2))} \times \left(E\left(X^2\right) - \sigma(X)^2\right) \\
&\equiv \frac{1}{(\Psi^*(X) \times E(X^2))} \times E(X)^2 \\
&\equiv \frac{1}{\Psi^*(X)} \times \frac{E(X)^2}{E(X^2)} \\
&\equiv \frac{1}{\Psi^*(X) \times X} \times E(X)
\end{aligned} \tag{17}$$

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).

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

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

$$E(\underline{X}) \equiv X - E(X) \equiv X - (X \times p(X)) \equiv X \times (+1 - p(X)) \tag{18}$$

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

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

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:

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

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

$$\begin{aligned} E(\underline{X})^2 &\equiv p(\underline{X}) \times X \times p(\underline{X}) \times X \\ &\equiv p(\underline{X}) \times p(\underline{X}) \times X \times X \\ &\equiv (p(\underline{X}) \times X)^2 \\ &\equiv E(\underline{X}) \times E(\underline{X}) \end{aligned} \tag{21}$$

Definition 2.8 (**The Second Moment Expectation of a Random Variable of $\underline{X}$ (anti X)**). *The second (see Kolmogorov, Andreĭ Nikolaevich, 1950, p. 42) moment expectation value (or more or less arithmetic mean) of a (large) number of independent realizations of a random variable anti X follows as:*

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

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

$$\begin{aligned} E(\underline{X}^n) &\equiv p(\underline{X}) \times X^n \\ &\equiv (p(\underline{X}) \times X) \times X^{n\text{-}1} \\ &\equiv E(\underline{X}) \times X^{n\text{-}1} \end{aligned} \tag{23}$$

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

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

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

In general, the co-variance is defined as given by equation 24.

$$\sigma(X,Y) \equiv E(X,Y) - (E(X) \times E(Y)) \tag{24}$$

From the point of view of tensor algebra, it is

$$\sigma\left(X_{kl\mu\nu\ldots}, Y_{kl\mu\nu\ldots}\right) \equiv E\left(X_{kl\mu\nu\ldots}, Y_{kl\mu\nu\ldots}\right) - \left(E\left(X_{kl\mu\nu\ldots}\right) \times E\left(Y_{kl\mu\nu\ldots}\right)\right) \tag{25}$$

2.2.2. Bernoulli distribution

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

Definition 2.11 (Two by two table of single event random variables).

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

In this context, let a random variable A at the *Bernoulli trial* (Uspensky, 1937) (period of time) t, denoted by A_t, indicate a risk factor, a condition, a cause et cetera and occur or exist with the probability

$p(A_t)$ at the *Bernoulli trial* (Uspensky, 1937) (period of time) t. Let $E(A_t)$ denote the expectation value of A_t. In general it is

$$p(A_t) \equiv p(a_t) + p(b_t) \tag{26}$$

The expectation value $E(A_t)$ follows as

$$\begin{aligned} E(A_t) &\equiv A_t \times p(A_t) \\ &\equiv A_t \times (p(a_t) + p(b_t)) \\ &\equiv (A_t \times p(a_t)) + (A_t \times p(b_t)) \\ &\equiv E(a_t) + E(b_t) \end{aligned} \tag{27}$$

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

$$\begin{aligned} E(A_t) &\equiv A_t \times p(A_t) \\ &\equiv (+0+1) \times p(A_t) \\ &\equiv p(A_t) \\ &\equiv p(a_t) + p(b_t) \end{aligned} \tag{28}$$

Furthermore, it is

$$p(\underline{A}_t) \equiv p(c_t) + p(d_t) \equiv (1 - p(A_t)) \tag{29}$$

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

$$\begin{aligned} E(\underline{A}_t) &\equiv A_t \times (1 - p(A_t)) \\ &\equiv A_t \times (p(c_t) + p(d_t)) \\ &\equiv (A_t \times p(c_t)) + (A_t \times p(d_t)) \\ &\equiv E(c_t) + E(d_t) \end{aligned} \tag{30}$$

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

$$\begin{aligned} E(\underline{A}_t) &\equiv A_t \times (1 - p(A_t)) \\ &\equiv (+0+1) \times (1 - p(A_t)) \\ &\equiv (1 - p(A_t)) \\ &\equiv p(c_t) + p(d_t) \end{aligned} \tag{31}$$

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

$$p(B_t) \equiv p(a_t) + p(c_t) \tag{32}$$

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

$$\begin{aligned} E(B_t) &\equiv B_t \times p(B_t) \\ &\equiv B_t \times (p(a_t) + p(c_t)) \\ &\equiv (B_t \times p(a_t)) + (B_t \times p(c_t)) \\ &\equiv E(a_t) + E(c_t) \end{aligned} \tag{33}$$

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

$$\begin{aligned} E\left(B_t\right) &\equiv B_t \times p\left(B_t\right) \\ &\equiv (+0+1) \times p\left(B_t\right) \\ &\equiv p\left(B_t\right) \\ &\equiv p\left(a_t\right) + p\left(c_t\right) \end{aligned} \tag{34}$$

Furthermore, it is

$$p\left(\underline{B}_t\right) \equiv p\left(b_t\right) + p\left(d_t\right) \equiv \left(1 - p\left(B_t\right)\right) \tag{35}$$

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

$$\begin{aligned} E\left(\underline{B}_t\right) &\equiv B_t \times \left(1 - p\left(B_t\right)\right) \\ &\equiv B_t \times \left(p\left(b_t\right) + p\left(d_t\right)\right) \\ &\equiv \left(B_t \times p\left(b_t\right)\right) + \left(B_t \times p\left(d_t\right)\right) \\ &\equiv E\left(b_t\right) + E\left(d_t\right) \end{aligned} \tag{36}$$

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

$$\begin{aligned} E\left(\underline{B}_t\right) &\equiv B_t \times \left(1 - p\left(B_t\right)\right) \\ &\equiv (+0+1) \times \left(1 - p\left(B_t\right)\right) \\ &\equiv \left(1 - p\left(B_t\right)\right) \\ &\equiv p\left(b_t\right) + p\left(d_t\right) \end{aligned} \tag{37}$$

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

$$\begin{aligned} E\left(a_t\right) &\equiv E\left(A_t \wedge B_t\right) \\ &\equiv \left(A_t \times B_t\right) \times p(A_t \wedge B_t) \\ &\equiv \left(A_t \times B_t\right) \times p(a_t) \end{aligned} \tag{38}$$

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

$$\begin{aligned} E\left(a_t\right) &\equiv E\left(A_t \wedge B_t\right) \\ &\equiv \left(A_t \times B_t\right) \times p(A_t \wedge B_t) \\ &\equiv \left((+0+1) \times (+0+1)\right) \times p(A_t \wedge B_t) \\ &\equiv p(A_t \wedge B_t) \\ &\equiv p\left(a_t\right) \end{aligned} \tag{39}$$

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

$$\begin{aligned} E\left(b_t\right) &\equiv E\left(A_t \wedge \neg B_t\right) \\ &\equiv \left(A_t \times \neg B_t\right) \times p(A_t \wedge \neg B_t) \\ &\equiv \left(A_t \times \neg B_t\right) \times p(b_t) \end{aligned} \tag{40}$$

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

$$\begin{aligned} E\left(b_t\right) &\equiv E\left(A_t \wedge \neg B_t\right) \\ &\equiv \left(A_t \times \neg B_t\right) \times p(A_t \wedge \neg B_t) \\ &\equiv ((+0+1) \times (+0+1)) \times p(A_t \wedge \neg B_t) \\ &\equiv p(A_t \wedge \neg B_t) \\ &\equiv p\left(b_t\right) \end{aligned} \tag{41}$$

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

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

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

$$\begin{aligned} E\left(c_t\right) &\equiv E\left(\neg A_t \wedge B_t\right) \\ &\equiv \left(\neg A_t \times B_t\right) \times p(\neg A_t \wedge B_t) \\ &\equiv ((+0+1) \times (+0+1)) \times p\left(\neg A_t \wedge B_t\right) \\ &\equiv p(\neg A_t \wedge B_t) \\ &\equiv p\left(c_t\right) \end{aligned} \tag{43}$$

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

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

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

$$\begin{aligned} E\left(d_t\right) &\equiv E\left(\neg A_t \wedge \neg B_t\right) \\ &\equiv \left(\neg A_t \times \neg B_t\right) \times p(\neg A_t \wedge \neg B_t) \\ &\equiv ((+0+1) \times (+0+1)) \times p\left(\neg A_t \wedge \neg B_t\right) \\ &\equiv p(\neg A_t \wedge \neg B_t) \\ &\equiv p\left(d_t\right) \end{aligned} \tag{45}$$

In general, it is

$$p\left(a_t\right) + p\left(b_t\right) + p\left(c_t\right) + p\left(d_t\right) \equiv +1 \tag{46}$$

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

In our understanding, it is

$$p\left(B_t\right) + p\left(\Lambda_t\right) \equiv p\left(a_t\right) + p\left(c_t\right) + p\left(\Lambda_t\right) \equiv p\left(a_t\right) + p\left(b_t\right) \equiv p\left(A_t\right) \tag{47}$$

Table 5. The two by two table of Bernoulli random variables

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

or

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

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

2.2.3. 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

$$p(X_t = k) \equiv \binom{n}{k} \cdot p^k \cdot q^{n-k} \tag{49}$$

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

$$p(X_t \leq k) \equiv 1 - p(X_t > k) \equiv \sum_{t=0}^{k} \binom{n}{t} \cdot p^t \cdot q^{n-t} \tag{50}$$

or as

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

Furthermore, it is

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

or

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

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

$$p\left(X_{\mathrm{t}}=k\right)\equiv p\cdot q^{k-1} \tag{54}$$

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

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

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

Definition 2.12 (Expectation value and variance of a binomial random variable).

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

$$\sigma\left(X_{\mathrm{t}}\right)^{2}\equiv N\times N\times p\left(X_{\mathrm{t}}\right)\times\left(1-p\left(X_{\mathrm{t}}\right)\right) \tag{56}$$

Definition 2.13 (Two by two table of Binomial random variables).

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

$$\begin{aligned}A&=N\times E\left(A_{\mathrm{t}}\right)\\&\equiv N\times\left(A_{\mathrm{t}}\times p\left(A_{\mathrm{t}}\right)\right)\\&\equiv N\times\left(p\left(A_{\mathrm{t}}\right)+p\left(B_{\mathrm{t}}\right)\right)\\&\equiv N\times p\left(A_{\mathrm{t}}\right)\end{aligned} \tag{57}$$

and

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

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

$$a\equiv N\times\left(E\left(A_{\mathrm{t}}\right)\right)\equiv N\times\left(p\left(A_{\mathrm{t}}\right)\right) \tag{59}$$

and

$$b \equiv N \times (E(B_t)) \equiv N \times (p(B_t)) \tag{60}$$

and

$$c \equiv N \times (E(c_t)) \equiv N \times (p(c_t)) \tag{61}$$

and

$$d \equiv N \times (E(d_t)) \equiv N \times (p(d_t)) \tag{62}$$

and

$$a+b+c+d \equiv A+\underline{A} \equiv B+\underline{B} \equiv N \tag{63}$$

Table 6 provide us again an overview of a two by two contingency (see also Pearson, 1904b, p. 33) table of Binomial random variables.

Table 6. The two by two table of Binomial random variables

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

"Such a table is termed a contingency table, and the ultimate scientific statement of description of the relation between two things can always be thrown back upon such a contingency table ⋯ Once the reader realizes the nature of such a table, he will have grasped the essence of the conception of association between cause and effect, and the nature of its ideal limit in causation. "

(see also Pearson, 1911, p. 159)

2.2.4. Independence

Definition 2.14 (Independence).

The philosophical, mathematical(Kolmogoroff, Andreĭ Nikolaevich, 1933) and physical(Einstein, 1948) et cetera concept of independence is of fundamental(Kolmogoroff, Andreĭ Nikolaevich, 1933) importance in (natural) sciences as such. Therefore, it is appropriate to investigate the concept of independence as completely as possible. In fact, de Moivre sums it up in his book The Doctrine of Chances (see also Moivre, 1718). "Two Events are **independent**, when they have no connexion one with the other, and that the happening of one neither forwards nor obstructs the happening of the other. Two events are **dependent**, when they are so connected together as that the Probability of either's happening is alter'd by the happening of the other. "(see also Moivre, 1756, p. 6) We should consider Kolmogorov's position on independence before the mind's eye too. "The concept

of mutual independence of two or more experiments holds, in a certain sense, a central position in the theory of probability."(see also Kolmogorov, Andreĭ Nikolaevich, 1950, p. 8) Furthermore, it is insightful to recall even Einstein's theoretical approach to the concept of independence. "*Ohne die Annahme einer ⋯ Unabhängigkeit der ⋯ Dinge voneinander ⋯ wäre physikalisches Denken ⋯ nicht möglich.*"(Einstein, 1948). In general, an event A_t at the Bernoulli trial t need not, but can be independent of the existence or of the occurrence, of another event B_t *at the same* Bernoulli trial t. De Moivre brings it to the point. "From what has been said, it follows, that if a Fraction expresses the Probability of an Event, and another Fraction the Probability of another Event, and those two Events are independent ; the Probability that both those Events will Happen, will be the Product of those two Fractions."(see also Moivre, 1718, p. 4). Mathematically, in terms of probability theory, independence (Kolmogoroff, Andreĭ Nikolaevich, 1933) of events at the same (period of) time (i.e. Bernoulli trial) t is defined as

$$\begin{aligned} p(A_t \wedge B_t) &\equiv p(A_t) \times p(B_t) \equiv p(a_t) \\ &\equiv \frac{\sum_{t=1}^{N} (A_t \wedge B_t)}{N} \equiv \frac{N \times (p(a_t))}{N} \equiv 1 - p(A_t \mid B_t) \equiv 1 - p(A_t \uparrow B_t) \end{aligned} \tag{64}$$

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

$$p(b_t) \equiv p(A_t) \times p(\underline{B}_t) \tag{65}$$

or

$$p(c_t) \equiv p(\underline{A}_t) \times p(B_t) \tag{66}$$

and

$$p(d_t) \equiv p(\underline{A}_t) \times p(\underline{B}_t) \tag{67}$$

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

2.2.5. Dependence

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

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

$$p\left(\underbrace{A_t \wedge B_t \wedge C_t \wedge \dots}_{n \text{ random variables}}\right) \equiv \sqrt[n]{\underbrace{p\left(A_t\right) \times p\left(B_t\right) \times p\left(C_t\right) \times \dots}_{n \text{ random variables}}} \tag{68}$$

2.2.6. Sensitivity and specificity

Definition 2.16 (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 [76] , [77] , [78] , [79] biostatistician Jacob Yerushalmy (see also Yerushalmy, 1947) in the year 1947. The interior logic of sensitivity and specificity is best illustrated using a conventional two- by-two (2 x 2) table (see table 7).

Table 7. Sensitivity and specificity

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

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

$$Sensitivity\,(A \mid B) \equiv p\,(a \mid B) \equiv \frac{a}{B} \tag{69}$$

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

$$Specificity\,(\underline{A},\underline{B}) \equiv p\,(d \mid \underline{B}) \equiv \frac{d}{\underline{B}} \tag{70}$$

The positive predictive value (PPV) is defined as

$$PPV\,(A,B) \equiv \frac{a}{a+b} \tag{71}$$

[76] 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.

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

[78] 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.

[79] 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

$$NPV\,(A,B) \equiv \frac{d}{c+d} \tag{72}$$

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 [80] of these measures. In the following, in order to avoid misconceptions about sensitivity, specificity et cetera, let us consider a test with a sensitivity of 95 % and a specificity of 95 %. A two-by-two table is used as an illustration (see table 8).

Table 8. Sensitivity and specificity

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

Sensitivity is calculated as

$$Sensitivity\,(A \mid B) \equiv p\,(a \mid B) \equiv 100 \times \frac{a}{B} \equiv \frac{95}{100} \equiv 95\% \tag{73}$$

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

$$SINE\,(A,B) \equiv 100 \times \frac{a+b+d}{N} \equiv \frac{95+5+95}{200} \equiv 97.5\% \tag{74}$$

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

$$Specificity\,(\underline{A} \mid \underline{B}) \equiv p\,(d \mid \underline{B}) \equiv 100 \times \frac{d}{\underline{B}} \equiv \frac{95}{100} \equiv 95\% \tag{75}$$

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

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

$$IMP(A,B) \equiv \frac{a+c+d}{N} \equiv \frac{95+5+95}{200} \equiv 97.5\% \tag{76}$$

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.

2.2.7. Odds ratio (OR)

Definition 2.17 (Odds ratio (OR))**.**

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

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

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

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

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

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

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

Hereafter, consider the table 9. The odds' ratio (OR) is defined as

Table 9. The two by two table of random variables

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

$$\begin{aligned} OR(A_t, B_t) &\equiv \left(\frac{a_t}{b_t}\right) / \left(\frac{c_t}{d_t}\right) \\ &\equiv \left(\frac{a_t \times d_t}{b_t \times c_t}\right) \end{aligned} \tag{77}$$

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

2.2.8. Relative risk (RR)

2.2.8.1. Relative risk (RR_{nc})

Definition 2.18 (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

$$\begin{aligned} RR(A_t,B_t)_{nc} &\equiv \frac{\frac{p(a_t)}{p(A_t)}}{\frac{p(c_t)}{p(NotA_t)}} \\ &\equiv \frac{p(a_t)\times p(NotA_t)}{p(c_t)\times p(A_t)} \\ &\equiv \frac{N\times p(a_t)\times N\times p(NotA_t)}{N\times p(c_t)\times N\times p(A_t)} \\ &\equiv \frac{a_t\times (NotA_t)}{c_t\times A_t} \\ &\equiv \frac{EER\,(A_t,B_t)}{CER\,(A_t,B_t)} \end{aligned} \tag{78}$$

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.

2.2.8.2. Relative risk (RR (sc))

Definition 2.19 (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

$$\begin{aligned} RR(A_t,B_t)_{sc} &\equiv \frac{\frac{p(a_t)}{p(B_t)}}{\frac{p(b_t)}{p(NotB_t)}} \\ &\equiv \frac{p(a_t)\times p(NotB_t)}{p(b_t)\times p(B_t)} \\ &\equiv \frac{N\times p(a_t)\times N\times p(NotB_t)}{N\times p(b_t)\times N\times p(B_t)} \\ &\equiv \frac{a_t\times (NotB_t)}{b_t\times B_t} \\ &\equiv \frac{OPR\,(A_t,B_t)}{CPR\,(A_t,B_t)} \end{aligned} \tag{79}$$

2.2.8.3. Relative risk reduction (RRR)

Definition 2.20 (Relative risk reduction (RRR))**.**

$$\begin{aligned} RRR\,(A_t,B_t) &\equiv \frac{CER\,(A_t,B_t)-EER\,(A_t,B_t)}{CER\,(A_t,B_t)} \\ &= 1-RR(A_t,B_t) \end{aligned} \tag{80}$$

2.2.8.4. Vaccine efficacy (VE)

Definition 2.21 (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.

$$\begin{aligned} VE\,(A_t,B_t) &\equiv 100\times (1-RR\,(A_t,B_t)) \\ &\equiv 100\times \left(\frac{CER\,(A_t,B_t)-EER\,(A_t,B_t)}{CER\,(A_t,B_t)}\right) \end{aligned} \tag{81}$$

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.

2.2.8.5. Experimental event rate (EER)

Definition 2.22 (Experimental event rate (EER))**.**

$$EER\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)\equiv\frac{p(a_{\mathrm{t}})}{p(A_{\mathrm{t}})}=\frac{a_{\mathrm{t}}}{a_{\mathrm{t}}+b_{\mathrm{t}}} \tag{82}$$

Definition 2.23 (Control event rate (CER))**.**

$$CER\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)\equiv\frac{p(c_{\mathrm{t}})}{p(\underline{A}_{\mathrm{t}})}=\frac{c_{\mathrm{t}}}{c_{\mathrm{t}}+d_{\mathrm{t}}} \tag{83}$$

2.2.8.6. Absolute risk reduction (ARR)

Definition 2.24 (Absolute risk reducation (ARR))**.**

$$\begin{aligned} ARR\left(A_{\mathrm{t}},B_{\mathrm{t}}\right) &\equiv \frac{p(c_{\mathrm{t}})}{p(\underline{A}_{\mathrm{t}})}-\frac{p(a_{\mathrm{t}})}{p(A_{\mathrm{t}})} \\ &= \frac{c_{\mathrm{t}}}{c_{\mathrm{t}}+d_{\mathrm{t}}}-\frac{a_{\mathrm{t}}}{a_{\mathrm{t}}+b_{\mathrm{t}}} \\ &= CER\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)-EER\left(A_{\mathrm{t}},B_{\mathrm{t}}\right) \end{aligned} \tag{84}$$

2.2.8.7. Absolute risk increase (ARI)

Definition 2.25 (Absolute risk increase (ARI))**.**

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

2.2.8.8. Number needed to treat (NNT)

Definition 2.26 (Number needed to treat (NNT))**.**

$$NNT\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)\equiv\frac{1}{CER\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)-EER\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)} \tag{86}$$

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.

2.2.8.9. Number needed to harm (NNH)

Definition 2.27 (Number needed to harm (NNH))**.**

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

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.

2.2.8.10. Outcome prevalence rate (OPR)

Definition 2.28 (Outcome prevalence rate (OPR))**.**

$$OPR\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)\equiv\frac{p(a_{\mathrm{t}})}{p(B_{\mathrm{t}})}=\frac{a_{\mathrm{t}}}{a_{\mathrm{t}}+c_{\mathrm{t}}} \tag{88}$$

2.2.8.11. Control prevalence rate (CPR)

Definition 2.29 (Control prevalence rate (CPR))**.**

$$CPR\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)\equiv\frac{p(b_{\mathrm{t}})}{p(\underline{B}_{\mathrm{t}})}=\frac{b_{\mathrm{t}}}{b_{\mathrm{t}}+d_{\mathrm{t}}} \tag{89}$$

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.

2.2.8.12. Absolute prevalence reduction (APR)

Definition 2.30 (Absolute prevalence reduction (APR))**.**

$$APR\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)\equiv CPR\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)-OPR\left(A_{\mathrm{t}},B_{\mathrm{t}}\right) \tag{90}$$

2.2.8.13. Absolute prevalence increase (API)

Definition 2.31 (Absolute prevalence increase (API))**.**

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

2.2.8.14. Relative prevalence reduction (RPR)

Definition 2.32 (Relative prevalence reduction (RPR))**.**

$$\begin{aligned} RPR\left(A_{\mathrm{t}},B_{\mathrm{t}}\right) &\equiv \frac{CPR\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)-OPR\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)}{CPR\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)} \\ &= 1-RR(A_{\mathrm{t}},B_{\mathrm{t}})_{\mathrm{sc}} \end{aligned} \tag{92}$$

2.2.8.15. The index NNS

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

$$NNS\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)\equiv\frac{1}{CPR\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)-OPR\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)} \tag{93}$$

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

2.2.8.16. The index NNI

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

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

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

2.2.9. 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

$$\begin{aligned} IOR(A_t, B_t) &\equiv \left(\frac{p(A_t \wedge B_t)}{p(B_t) \times p(A_t)} \right) - 1 \\ &\equiv \left(\frac{p(a_t)}{p(B_t) \times p(A_t)} \right) - 1 \\ &\equiv \left(\left(\frac{N \times N \times p(a_t)}{N \times p(B_t) \times N \times p(A_t)} \right) - 1 \right) \\ &\equiv \left(\left(\frac{N \times a}{A \times B} \right) - 1 \right) \end{aligned} \tag{95}$$

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

2.3. Conditions

2.3.1. Exclusion relationship

Definition 2.36 (Exclusion relationship [*EXCL*]).

Mathematically, the exclusion(see also Barukčić, 2021a) relationship [81] (EXCL), denoted by $p(A_t \mid B_t)$ in terms of statistics and probability theory, is defined(see also Barukčić, 1989, p. 68-70) as

$$\begin{aligned} p(A_t \mid B_t) &\equiv p(A_t \uparrow B_t) \\ &\equiv p(b_t) + p(c_t) + p(d_t) \\ &\equiv \frac{N \times (p(b_t) + p(c_t) + p(d_t))}{N} \\ &\equiv \frac{\sum_{t=1}^{N} (\underline{A}_t \vee \underline{B}_t)}{N} \equiv \frac{b+c+d}{N} \\ &\equiv \frac{b+\underline{A}}{N} \\ &\equiv \frac{c+\underline{B}}{N} \\ &\equiv +1 \end{aligned} \tag{96}$$

Based on the 1913 Henry Maurice Sheffer (1882-1964) relationship, the Sheffer stroke(Nicod, 1917, Sheffer, 1913) usually denoted by $\uparrow$, it is $p(A_t \wedge B_t) \equiv 1 - p(A_t \mid B_t)$ (see table 10).

Table 10. A_t excludes B_t and vice versa.

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

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

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

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

$$\begin{aligned} p\left(Vaccine : BNT162b2 \mid COVID-19(infection)\right) &\equiv p\left(b_t\right)+p\left(c_t\right)+p\left(d_t\right) \\ &\equiv 1-p\left(a_t\right) \\ &\equiv 1-\left(\frac{8}{43538}\right) \\ &\equiv +0,99981625 \end{aligned} \tag{97}$$

with a P Value = 0,000184.

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

$$\begin{aligned} p\left(A_{\mathrm{t}} \mid B_{\mathrm{t}}\right) &\equiv p\left(\underline{A}_{\mathrm{t}} \cup \underline{B}_{\mathrm{t}}\right) \\ &\equiv 1-p\left(A_{\mathrm{t}} \cap B_{\mathrm{t}}\right) \\ &\equiv 1-\int_{-\infty}^{A_{\mathrm{t}}} \int_{-\infty}^{B_{\mathrm{t}}} f\left(A_{\mathrm{t}}, B_{\mathrm{t}}\right)\, dA_{\mathrm{t}}\, dB_{\mathrm{t}} \\ &\equiv +1 \end{aligned} \tag{98}$$

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

2.3.2. Observational study and exclusion relationship

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

$$p\left(A_{\mathrm{t}} \mid B_{\mathrm{t}}\right) \equiv p\left(A_{\mathrm{t}} \uparrow B_{\mathrm{t}}\right) \geq 1-\frac{p\left(a_{\mathrm{t}}\right)}{p\left(B_{\mathrm{t}}\right)} \tag{99}$$

2.3.3. Experimental study and exclusion relationship

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

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

2.3.4. 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

$$\begin{aligned}\tilde{\chi}^2{}_{\text{Calculated}}\left((A_t \mid B_t) \mid A\right) &\equiv \frac{(b-(a+b))^2}{A}+ \\ &\quad \frac{((c+d)-\underline{A})^2}{\underline{A}} \\ &\equiv \frac{a^2}{A}+0 \\ &\equiv \frac{a^2}{A}\end{aligned} \tag{101}$$

or equally as

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

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

2.3.5. 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, 2019d) of an exclusion relationship can be calculated as follows.

$$\begin{aligned}pValue_{\text{lt}}\left(A_t \mid B_t\right) &\equiv 1-e^{-(1-p(A_t|B_t))} \\ &\equiv 1-e^{-(a/N)}\end{aligned} \tag{103}$$

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

2.3.6. 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

$$\begin{aligned} p\left(A_t \downarrow B_t\right) &\equiv p\left(d_t\right) \\ &\equiv \frac{N - \sum_{t=1}^{N} \left(A_t \vee B_t\right)}{N} \equiv \frac{\sum_{t=1}^{N} \left(\underline{A}_t \wedge \underline{B}_t\right)}{N} \equiv \frac{N \times \left(p\left(d_t\right)\right)}{N} \\ &\equiv \frac{d}{N} \\ &\equiv +1 \end{aligned} \tag{104}$$

2.3.7. 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

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

or equally as

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

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

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

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

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

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

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 11).

Table 11. Neither A_t nor B_t relationship.

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

2.3.9. 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[82]. It comes therefore as no surprise that one of the first documented attempts to present a rigorous theory of conditions and causation (see also Aristotle, of Stageira (384-322 B.C.E), 1908, Metaphysica III 2 997a 10 and 13/14) came from the Greek philosopher and scientist Aristotle (384-322 BCE). Thus far, it is amazing that Aristotle himself made already a strict distinction between conditions and causes. Taking Aristotle very seriously, it is necessary to consider that

> "... everything which has a ... ... potency in question ... ... has the potency ... of acting ... not in all circumstances but on certain conditions ... " (see also Aristotle, of Stageira (384-322 B.C.E), 1908, Metaphysica IX 5 1048a 14-19)

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

> "... necessary ... means ...
>
> without ... a condition, a thing cannot live ... "
>
> (see also Aristotle, of Stageira (384-322 B.C.E), 1908, Metaphysica V 2 1015a 20-22)

In point of fact, Aristotle developed a theory of conditions and causality commonly referred to as the doctrine of four causes. Many aspects and general features of Aristotle's logical concept of causality are meanwhile extensively and critically debated in secondary literature. However, even if the Greek philosophers Heraclitus, Plato, Aristotle et cetera numbers among the greatest philosophers of all time, the philosophy has evolved. Scientific knowledge and objective reality are deeply interrelated and cannot be reduced only to Greek philosophers like Aristotle. Among many other issues, the specification of necessary conditions has traditionally been part of the philosopher's investigations of different phenomena. However, behind the need of a detailed evidence, it is justified to consider that philosophy or philosophers as such certainly do not possess **a monopoly on the truth** and other areas such as medicine as well as other sciences and technology may transmit truths as well and may be of help to move beyond one's self enclosed unit. Seemingly, **the law's concept of causation** justifies to say few words on this subject, to put some light on some questions. Are there any criteria in law for deciding whether one action or an event A_t has caused another (generally harmful) event B_t? What are these criteria? May causation in legal contexts differ from causation outside the law, for example, in science

[82] Barukčić, Ilija. (2022). Conditio sine qua non (Version 1). Zenodo. https://doi.org/10.5281/zenodo.5854744

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

$$\begin{aligned} p\left(A_t \leftarrow B_t\right) \equiv p\left(A_t \vee \underline{B}_t\right) &\equiv \frac{\sum_{t=1}^{N}\left(A_t \vee \underline{B}_t\right)}{N} \equiv \frac{\left(A_t \vee \underline{B}_t\right) \times p\left(A_t \vee \underline{B}_t\right)}{\left(A_t \vee \underline{B}_t\right)} \\ &\equiv p\left(a_t\right) + p\left(b_t\right) + p\left(d_t\right) \\ &\equiv \frac{N \times \left(p\left(a_t\right) + p\left(b_t\right) + p\left(d_t\right)\right)}{N} \equiv \frac{E\left(A_t \leftarrow B_t\right)}{N} \\ &\equiv \frac{a+b+d}{N} \equiv \frac{E\left(A_t \vee \underline{B}_t\right)}{N} \\ &\equiv \frac{A+d}{N} \equiv \frac{E\left(A_t \leftarrow B_t\right)}{N} \\ &\equiv \frac{a+\underline{B}}{N} \equiv \frac{E\left(A_t \vee \underline{B}_t\right)}{N} \\ &\equiv +1 \end{aligned} \tag{108}$$

where $E\left(A_t \leftarrow B_t\right) \equiv E\left(A_t \vee \underline{B}_t\right)$ indicates the expectation value of the necessary condition. In general, it is $p\left(A_t \prec B_t\right) \equiv 1 - p\left(A_t \leftarrow B_t\right)$ (see Table 12).

Table 12. Necessary condition.

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

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, 2020a,b,c,d, Barukčić and Ufuoma, 2020). Taking into account Kolmogorov's definition of an n-dimensional probability density (see also Kolmogorov, Andreĭ Nikolaevich, 1950, p. 26) of random variables A_t, B_t et cetera at the (period of) time t, we obtain

$$\begin{aligned} p\left(A_t \leftarrow B_t\right) &\equiv +1 \\ &\equiv +1 - p\left(c_t\right) \\ &\equiv +1 - p\left(\underline{A}_t \cap B_t\right) \\ &\equiv \left(\int_{-\infty}^{A_t}\int_{-\infty}^{B_t} f\left(A_t, B_t\right)\, dA_t\, dB_t\right) + \left(1 - \int_{-\infty}^{B_t} f\left(B_t\right)\, dB_t\right) \end{aligned} \tag{109}$$

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

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

$$p\left(A_t \leftarrow B_t\right) \equiv \underbrace{\left(A_t \vee \underline{B}_t\right)}_{\text{(Necessary condition)}} \equiv \underbrace{\left(\underline{B}_t \vee A_t\right)}_{\text{(Sufficient condition)}} \equiv p\left(B_t \rightarrow A_t\right) \tag{110}$$

These relationships are illustrated by the following tables.

Table 13. Without A_t no B_t

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

Table 14. If B_t then A_t

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

There are circumstances under which

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

However, equation 110 does not imply the relationship of equation 111 under any circumstances.

Example I.

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

Table 15. Without gaseous oxygen no burning candle

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

Table 16. If burning candle then gaseous oxygen

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

Example II.

Once again, a human being cannot live without water. A human being cannot live without gaseous oxygen, et cetera. Water itself is a necessary condition for human life. However, gaseous oxygen is a necessary condition for human life too. Thus far, even if water is given and even if water is a necessary condition for human life, without gaseous oxygen there will be no human life. In general, if a conditioned or an outcome B_t depends on the necessary condition A_t and equally on numerous other

necessary conditions, an event B_t will not occur if A_t itself is not given independently of the occurrence of other necessary conditions.

Example III.

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

Table 17. Without gaseous oxygen no burning candle

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

Table 18. Absent gaseous oxygen excludes burning wax candle

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

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

$$p\left(A_t \leftarrow B_t\right) \geq 1 - \frac{p\left(c_t\right)}{p\left(B_t\right)} \tag{112}$$

and as

$$p\left(A_t \leftarrow B_t\right) \geq 1 - \frac{p\left(c_t\right)}{p\left(\underline{A}_t\right)} \tag{113}$$

2.3.10. 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

$$\begin{aligned}\tilde{\chi}^2{}_{\text{Calculated}}\left(A_{\text{t}} \leftarrow B_{\text{t}} \mid B\right) &\equiv \frac{\left(a-(a+c)\right)^2}{B}+ \\ &\quad \frac{\left((b+d)-\underline{B}\right)^2}{\underline{B}} \\ &\equiv \frac{c^2}{B}+0 \\ &\equiv \frac{c^2}{B}\end{aligned} \tag{114}$$

or equally as

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

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

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

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

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

$$\begin{aligned}pValue_{\text{lt}}\left(A_{\text{t}} \leftarrow B_{\text{t}}\right) &\equiv 1-e^{-\left(1-p\left(A_{\text{t}} \leftarrow B_{\text{t}}\right)\right)} \\ &\equiv 1-e^{-(c/N)}\end{aligned} \tag{116}$$

2.3.12. Sufficient condition

Definition 2.45 (**Sufficient condition [*Conditio per quam*]**).

Mathematically, the sufficient (Barukčić, 2021c, p. 68-70) condition (IMP) relationship, denoted by $p(A_t \rightarrow B_t)$ in terms of statistics and probability theory, is defined (Barukčić, 1989, p. 68-70) as

$$\begin{aligned} p\left(A_t \rightarrow B_t\right) \equiv p\left(\underline{A}_t \vee B_t\right) &\equiv \frac{\sum_{t=1}^{N}\left(\underline{A}_t \vee B_t\right)}{N} \equiv \frac{\left(\underline{A}_t \vee B_t\right) \times p\left(\underline{A}_t \vee B_t\right)}{\left(\underline{A}_t \vee B_t\right)} \\ &\equiv p\left(a_t\right) + p\left(c_t\right) + p\left(d_t\right) \\ &\frac{N \times \left(p\left(a_t\right) + p\left(c_t\right) + p\left(d_t\right)\right)}{N} \\ &\equiv \frac{a+c+d}{N} \equiv \frac{E\left(\underline{A}_t \vee B_t\right)}{N} \\ &\equiv \frac{B+d}{N} \equiv \frac{E\left(A_t \rightarrow B_t\right)}{N} \\ &\equiv \frac{a+\underline{A}}{N} \\ &\equiv +1 \end{aligned} \tag{117}$$

In general, it is $p\left(A_t \succ\!\!- B_t\right) \equiv 1 - p\left(A_t \rightarrow B_t\right)$ (see Table 19). There are circumstances, where several different events [83] might be necessary at the same time in order to determine **a compound sufficient condition relationship**. Equation 118 illustrates this case in more detail.

$$\begin{aligned} p\left(\left(\left({}_1X_t \wedge {}_2X_t \wedge {}_3X_t \wedge \cdots\right) \wedge A_t\right) \rightarrow B_t\right) &\equiv p\left(\underline{\left(\left({}_1X_t \wedge {}_2X_t \wedge {}_3X_t \wedge \cdots\right) \wedge A_t\right)} \vee B_t\right) \\ &\equiv \frac{\sum_{t=1}^{N}\left(\underline{\left(\left({}_1X_t \wedge {}_2X_t \wedge {}_3X_t \wedge \cdots\right) \wedge A_t\right)} \vee B_t\right)}{N} \\ &\equiv +1 \end{aligned} \tag{118}$$

Again, 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

$$\begin{aligned} p\left(A_t \rightarrow B_t\right) &\equiv +1 \\ &\equiv +1 - p\left(b_t\right) \\ &\equiv +1 - p\left(A_t \cap \underline{B}_t\right) \\ &\equiv \left(\int_{-\infty}^{A_t}\int_{-\infty}^{B_t} f\left(A_t, B_t\right)\, dA_t\, dB_t\right) + \left(1 - \int_{-\infty}^{A_t} f\left(A_t\right)\, dA_t\right) \end{aligned} \tag{119}$$

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

[83] Barukčić, Ilija. (2022). Conditio per quam. Causation, 17(3), 5–86. https://doi.org/10.5281/zenodo.6369831

Table 19. Sufficient condition.

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

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

$$p\left(A_t \rightarrow B_t\right) + p\left(R_t \wedge B_t\right) \equiv +1 \tag{120}$$

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

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

$$p\left(A_t \rightarrow B_t\right) \geq 1 - \frac{p\left(b_t\right)}{p\left(A_t\right)} \tag{121}$$

and alternatively as

$$p\left(A_t \rightarrow B_t\right) \geq 1 - \frac{p\left(b_t\right)}{p\left(\underline{B}_t\right)} \tag{122}$$

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

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

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.

2.3.14. 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, 2019d) 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.

2.3.15. 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

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

2.3.16. 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.

2.3.17. 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, 2019d) of a necessary and sufficient condition relationship can be calculated as follows.

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

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

Table 20. Necessary and sufficient condition.

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

2.3.18. 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

$$\begin{aligned} p\left(A_{\mathrm{t}} \succ\!\prec B_{\mathrm{t}}\right) &\equiv \frac{\sum_{t=1}^{N}\left(\left(A_{\mathrm{t}} \wedge \underline{B}_{\mathrm{t}}\right) \vee \left(\underline{A}_{\mathrm{t}} \wedge B_{\mathrm{t}}\right)\right)}{N} \\ &\equiv p\left(b_{\mathrm{t}}\right)+p\left(c_{\mathrm{t}}\right) \\ &\equiv \frac{N \times \left(p\left(b_{\mathrm{t}}\right)+p\left(c_{\mathrm{t}}\right)\right)}{N} \\ &\equiv \frac{b+c}{N} \\ &\equiv +1 \end{aligned} \tag{130}$$

It is $p\left(A_{\mathrm{t}} \succ\!\prec B_{\mathrm{t}}\right) \equiv 1-p\left(A_{\mathrm{t}} <\!\!> B_{\mathrm{t}}\right)$ (see Table 21).

Table 21. Either A_t or B_t relationship.

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

2.3.19. 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

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

or equally as

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

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

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

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

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

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

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

2.3.21. Causal relationship k

The history of the denialism of causality in Philosophy, Mathematics, Statistics, Physics et cetera is very long. We only recall David Hume's (1711-1776) account of causation and his inappropriate reduction of the cause-effect relationship to a simple habitual connection in human thinking or Immanuel Kant's (1724-1804) initiated trial to consider causality as nothing more but a '*a priori*'given category (Langsam, 1994) in human reasoning and other similar attempts too.

It is worth noting in this context that especially Karl Pearson (1857 - 1936) himself has been engaged in a long lasting and never-ending crusade against causation too. "**Pearson categorically denies the need for an independent concept of causal relation beyond correlation ... he *exterminated* causation from statistics before it had a chance to take root** "(see Pearl, 2000, p. 340).

At the beginning of the 20th century notable proponents of **conditionalism** like the German anatomist and pathologist David Paul von Hansemann (Hansemann, David Paul von, 1912) (1858 - 1920) and the biologist and physiologist Max Richard Constantin Verworn(Verworn, 1912) (1863 - 1921) started a new attack(Kröber, 1961) on the principle of causality. In his essay "Kausale und konditionale Weltanschauung"Verworn(Verworn, 1912) presented "an exposition of 'conditionism'as contrasted with 'causalism,'(Unknown, 1913) while ignoring cause and effect relationships completely. "**Das Ding ist also identisch mit der Gesamtheit seiner Bedingungen**."(Verworn, 1912) However, Verworn's goal to exterminate causality completely out of science was hindered by the further development of research.

The history of futile attempts to refute **the principle of causality** culminated in a publication by the German born physicist Werner Karl Heisenberg (1901 - 1976). Heisenberg put forward an illogical, inconsistent and confusing uncertainty principle which opened the door to wishful thinking and logical fallacies in physics and in science as such. Heisenberg's unjustified reasoning ended in an act of a manifestly unfounded conclusion: "**Weil alle Experimente den Gesetzen der Quantenmechanik und damit der Gleichung (1) unterworfen sind, so wird durch die Quantenmechanik die Ungültigkeit des Kausalgesetzes definitiv festgestellt**."(Heisenberg, Werner Karl, 1927) while 'Gleichung (1)'denotes Heisenberg's uncertainty principle. Einstein's himself, a major contributor to quantum theory and in the same respect a major critic of quantum theory, disliked Heisenberg's uncertainty principle fundamentally while Einstein's opponents used Heisenberg's Uncertainty Principle against Einstein. After the End of the German Nazi initiated Second World War with unimaginable brutality and high human losses and a death toll due to an industrially organised mass killing of people by the German Nazis which did not exist in this way before, Werner Heisenberg visited Einstein in Princeton (New Jersey, USA) in October 1954 (Neffe, 2006). Einstein agreed to meet Heisenberg only for a very short period of time but their encounter lasted longer. However, there where not only a number of differences between Einstein and Heisenberg, these two physicists did not really loved each other. "Einstein remarked that the inventor of the uncertainty principle was a 'big Nazi'... "(Neffe, 2006) Albert Einstein (1879 - 1955) took again the opportunity to refuse to endorse **Heisenberg's uncertainty principle** as a fundamental law of nature and rightly too. Meanwhile, Heisenberg's uncertainty principle is refuted (see Barukčić, 2011a, 2014, 2016a) for several times but still not exterminated completely out of physics and out of science as such.

In contrast to such extreme anti-causal positions as advocated by Heisenberg and the **Copenhagen interpretation of quantum mechancis**, the search for a (mathematical) solution of *the issue of causal inferences* is as old as human mankind itself ("*i. e. Aristotle's Doctrine of the Four Causes*") (Hennig, 2009) even if there is still little to go on.

It is appropriate to specify especially the position of D'Holbach(Holbach, Paul Henri Thiry Baron de, 1770). D'Holbach (1723-1789) himself linked cause and effect or causality as such to changes. "**Une *cause*, est un être qui e met un autre en mouvement, ou qui produit quelque changement en lui. *L'effet* est le changement qu'un corps produit dans un autre ...**"(Holbach, Paul Henri Thiry Baron de, 1770). D'Holbach infers in the following: "**De l'action et de la réaction continuelle de tous les êtres que la nature renferme, il résulte une suite de causes et d'effets ...**"(Holbach, Paul Henri Thiry Baron de, 1770).

With more or less meaningless or none progress on the matter in hand even in the best possible conditions, it is not surprising that authors are suggesting more and more different approaches and models for causal inference. Indeed, the hope is justified that logically consistent *statistical methods of causal inference* can help scientist to achieve so much with so little.

One of the methods of causal inference in Bio-sciences are based on the known *Henle(Henle, 1840) (1809–1885) - Koch(Koch, 1878) (1843–1910) postulates* (Carter, 1985) which are applied especially for the identification of a causative agent of an (infectious) disease. However, the pathogenesis of most chronic diseases is more or less very complex and potentially involves the interaction of several factors. In practice, from the 'pure culture' requirement of the Henle-Koch postulates insurmountable difficulties may emerge. In light of subsequent developments (PCR methodology, immune antibodies et cetera) it is appropriate to review the full validity of the Henle-Koch postulates in our days.

In 1965, Sir Austin Bradford Hill (Hill, 1965) published nine criteria (the '*Bradford Hill Criteria* ') in order to determine whether observed 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 [84] , [85] as

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

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

Table 22. Sample space and the causal relationship k

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

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

[84] Ilija Barukčić, "The Mathematical Formula of the Causal Relationship k," International Journal of Applied Physics and Mathematics vol. 6, no. 2, pp. 45-65, 2016. https://doi.org/10.17706/ijapm.2016.6.2.45-65

[85] Barukčić, Ilija. (2015). The Mathematical Formula Of The Causal Relationship k. https://doi.org/10.5281/zenodo.3944666

2.3.22. 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 23 may illustrate this relationship.

Table 23. What is the cause, what is the effect?

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

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

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

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.

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

2.4. 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.

2.4.1. Lex identitatis (Axiom I)

Lex identitatis or axiom I, is closely related to central problems of metaphysics, epistemology and of science as such. It turns out that it is more than rightful to assume and to accept without any doubt that

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

is true otherwise there is every good reason to suppose that nothing could be discovered at all.

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

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

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

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

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

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

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

> "**Each thing is what it is ;**

it has those realities which are posited when it is posited,
(A = A.) ”
(Fichte, 1889)

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

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

(see Russell, 1912, p. 113)

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

2.4.2. Lex contradictionis (Axiom II)

Lex contradictionis [86] , [87] , [88] or axiom II, the other of lex identitatis, the negative of lex identitatis, the opposite of lex identitatis, the complementary of lex identitatis, can be expressed mathematically as

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

[86] Horn, Laurence R., "Contradiction", The Stanford Encyclopedia of Philosophy (Winter 2018 Edition), Edward N. Zalta (ed.), URL = https://plato.stanford.edu/archives/win2018/entries/contradiction/.
[87] Barukčić I. Aristotle's law of contradiction and Einstein's special theory of relativity. Journal of Drug Delivery and Therapeutics (JDDT). 15Mar.2019;9(2):125-43. https://jddtonline.info/index.php/jddt/article/view/2389
[88] Barukčić, Ilija. (2020, December 28). The contradiction is exsiting objectively and real (Version 1). Zenodo. https://doi.org/10.5281/zenodo.4396106

In addition to the above, axiom II (equation 140) is equally the most simple form of a contradiction formulated mathematically. However, sometimes mathematical knowledge appears to differ from the knowledge in the natural sciences.

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.

2.4.3. Lex negationis (Axiom III)

Lex negationis or axiom III, is often mismatched with simple opposition. However, from the point of view of philosophy and other sciences, identity, contradiction, negation and similar notions are equally mathematical descriptions of the most simple laws of objective reality. What sort of natural process is negation at the end? Mathematically, we define lex negationis or axiom III as

$$\frac{1}{0} \times 0 \equiv \frac{0}{0} \equiv \neg(0) \times 0 \equiv +1 \tag{141}$$

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, the Categories, De Interpretatione, and the Prior Analytics (see also Horn, 1989, p. 1). Negation (see also Newstadt, 2015) as a fundamental philosophical concept found its own very special melting point especially in Hegel's dialectic and is more than just a formal logical process or operation which converts true to false or 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 creation and conservation or 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. Why and how does an event occur or why and how is an event created (creation), why and how does an event maintain its own existence over time (conservation)? The development of the notion of negation leads from Aristotle to Meister Eckhart (see also Eckhart, 1986) von Hochheim (1260-1328), commonly known as Meister Eckhart (see also Tsopurashvili, 2012) or Eckehart, to Spinoza (1632 – 1677), to Immanuel Kant (1724-1804) and finally to Georg Wilhelm Friedrich Hegel (1770-1831) and other authors too. One point is worth being noted, even if it does not come as a surprise, it was especially Benedict de Spinoza (1632 – 1677) as one of the philosophical founding fathers of the Age of Enlightenment who addressed the relationship between determination and negation in his lost letter of June 2, 1674 to his friend Jarig Jelles (see also Förster and Melamed, 2012) by the discovery of his fundamental insight that " **determinatio negatio est**" (see also Spinoza, 1674, p. 634). Hegel went even so far as to extended the slogan raised by Spinoza into to "Omnis determinatio est negatio" (see also Hegel, Georg Wilhelm Friedrich, 1812b, 2010, p. 87). Finally, it did not take too long, and the notion of negation entered the world of mathematics and mathematical logic at least with Boole's (see also Boole, 1854) publication in the year 1854. "Let us, for simplicity of conception, give to the symbol x the particular interpretation of men, then 1 - x will represent the class of 'not-men'." (see also Boole, 1854, p. 49). Finally, the philosophical notion negation found its own way into physics by the contributions of authors like Woldemar Voigt (see Voigt, 1887), George Francis FitzGerald (see FitzGerald, 1889), Hendrik Antoon Lorentz (see Lorentz, 1892, 1899), Joseph Larmor (see Larmor, 1897), Jules Henri Poincaré (see Poincaré, 1905) and Albert Einstein (see Einstein, 1905) by contributions to the physical notion "Lorentz factor".

3. Results

3.1. EBV IgG and BC: The study of Mashaly et al., 2022

Mashaly et al. [89] investigated the relationship between EBV and BC.

Table 24. EBV VCA IgG and BC .

		BC		
		YES	NO	
EBV VCA IgG	YES	120	180	300
	NO	22	40	62
		142	220	362

STATISTICAL ANALYSIS.

p(IOU)=	0,220994475
Causal relationship k =	0,0348471529
p (SINE) =	0,9392265193
$\tilde{\chi}^2$ (SINE — B_t) =	3,4085
$\tilde{\chi}^2$ (SINE — $\underline{A}_t$) =	7,8065
p Value right tailed (HGD) =	0,3034
p Value (SINE) =	0,0589636214
RR (nc) =	1,1273
RR (sc) =	1,0329
OR =	1,2121
IOR =	0,0197

The prevalence of EBV VCA IgG in the group of cases is given as $\frac{120}{142} \times 100 = 84,5\%$. The prevalence of EBV VCA IgG in the group of controls is given as $\frac{180}{220} \times 100 = 81,8\%$ .The data of the study of Mashaly et al. are underestimating the prevalence of EBV VCA IgG in the population (see table 2, p. 11). As a consequence, the data of the study of Mashaly et al. are biased at least to some extent. In reality, the relationship between EBV VCA IgG and BC is much stronger than these data do suggest. The index of independence is p(IOU)= 0,221 (see Barukčić, 2019c, p. 25). The study design of the study of Mashaly et al. is The study design of the study of Mashaly et al. unfair (see table 3, p. 14). Therefore, the data are only of some restricted value. The causal relationship k is positive, the data are not self-contradictory. The necessary condition relationship between EBV VCA IgG and BC is given as $\frac{120+180+40}{362} = 0,939226519.$. Considered in all aspects, the result is statistically significant. In other words, **without** EBV VCA IgG **no** BC (P Value = 0,058963621).

[89]Mashaly M, Ghorab D, Hegazy M, Abdelkhalek M, Gaballah K, Elzehery R. Association between Epstein-Barr Virus Gene Polymorphism and Breast Cancer Risk among Egyptian Females. Asian Pac J Cancer Prev. 2022 Feb 1;23(2):641-650. doi: 10.31557/APJCP.2022.23.2.641. PMID: 35225477.

3.2. *EBV IgG and BC: The study of Richardson et al., 2015*

Richardson et al. [90] investigated the relationship between EBV and BC but did not provide an appropriate control group. In the following, we used a fictive control group.

Table 25. EBV VCA IgG and BC.

		BC		
		YES	NO	
EBV VCA IgG	YES	67	1334	1401
	NO	3	66	69
		70	1400	1470

STATISTICAL ANALYSIS.

p(IOU)=	0,000680272
Causal relationship k =	0,0043151176
p (SINE) =	0,9979591837
$\tilde{\chi}^2$ (SINE — B_t) =	0,1286
$\tilde{\chi}^2$ (SINE — $\underline{A}_t$) =	0,1304
p Value right tailed (HGD) =	0,5807
p Value (SINE) =	0,0020387353
RR (nc) =	1,0999
RR (sc) =	1,0045
OR =	1,1049
IOR =	0,0043

The **prevalence** of EBV VCA IgG in the group of cases is given as $\frac{67}{70} \times 100 = 95,7\%$. The **prevalence** of EBV VCA IgG in the group of controls is estimated as $\frac{1334}{1400} \times 100 = 95,3\%$. The data of this fictive control group is not underestimating the prevalence of EBV VCA IgG in the population (see table 2, p. 11). The index of independence is p(IOU)= 0,001 (see Barukčić, 2019c, p. 25). The study design of the study of Richardson et al. is unfair (see table 3, p. 14). However, because of the fictive control group, the data are only of some restricted value. The causal relationship k is positive, the data are not self-contradictory. The necessary condition relationship between EBV VCA IgG and BC is given as $\frac{67+1334+66}{1470} = 0,997959184.$. Considered in all aspects, the result is statistically significant. In other words, **without** EBV VCA IgG **no** BC (P Value = 0,002038735) .

[90] Richardson AK, Currie MJ, Robinson BA, Morrin H, Phung Y, Pearson JF, Anderson TP, Potter JD, Walker LC. Cytomegalovirus and Epstein-Barr virus in breast cancer. PLoS One. 2015 Feb 27;10(2):e0118989. doi: 10.1371/journal.pone.0118989. PMID: 25723522; PMCID: PMC4344231.

3.3. EBV IgG and BC: The study of Agborsangaya et al.

Agborsangaya et al. [91] investigated the relationship between EBV and BC. It was not possible to consider this study for further analysis. Reason: Data access barriers.

[91] Agborsangaya CB, Lehtinen T, Toriola AT, Pukkala E, Surcel HM, Tedeschi R, Lehtinen M. Association between Epstein-Barr virus infection and risk for development of pregnancy-associated breast cancer: joint effect with vitamin D? Eur J Cancer. 2011 Jan;47(1):116-20. doi: 10.1016/j.ejca.2010.07.006. Epub 2010 Aug 4. PMID: 20691583.

3.4. EBV IgG and BC: The study of He et al.

He et al. [92] investigated the relationship between EBV and BC. It was not possible to consider this study for further analysis. Reason: Data access barriers.

[92] He JR, Tang LY, Yu DD, Su FX, Song EW, Lin Y, Wang SM, Lai GC, Chen WQ, Ren ZF. Epstein-Barr virus and breast cancer: serological study in a high-incidence area of nasopharyngeal carcinoma. Cancer Lett. 2011 Oct 28;309(2):128-36. doi: 10.1016/j.canlet.2011.05.012. Epub 2011 Jun 24. PMID: 21724319.

3.5. EBV IgG and BC: The study of Cox et al.

Cox et al. [93] investigated the relationship between EBV and BC. When the second sample has been taken 386 (96.7%) of cases were EBV seropositive compared with 384 (96.2%) of the controls.

Table 26. EBV VCA IgG and BC.

		BC		
		YES	NO	
EBV VCA IgG	YES	386	384	770
	NO	13	15	28
		399	399	798

STATISTICAL ANALYSIS.

p(IOU)=	0,464912281
Causal relationship k =	0,0136208941
p (SINE) =	0,9837092732
$\tilde{\chi}^2$ (SINE — B_t) =	0,4236
$\tilde{\chi}^2$ (SINE — $\underline{A}_t$) =	6,0357
p Value right tailed (HGD) =	0,4239
p Value (SINE) =	0,0161587506
RR (nc) =	1,0797
RR (sc) =	1,0052
OR =	1,1599
IOR =	0,0026

The **prevalence** of EBV VCA IgG in the group of cases is given as $\frac{386}{399} \times 100 = 96,7\%$. The **prevalence** of EBV VCA IgG in the group of controls is given as $\frac{384}{399} \times 100 = 96,2\%$. The data of the study of Cox et al. are not underestimating the prevalence of EBV VCA IgG in the population (see table 2, p. 11). The index of independence is p(IOU)= 0,465 (see Barukčić, 2019c, p. 25). The study design of the study of Cox et al. is very unfair (see table 3, p. 14). Therefore, the data are only of some restricted value. As a consequence, the data of the study of Cox et al. are biased, at least to some extent. In reality, the relationship between EBV VCA IgG and BC is much stronger than these data do suggest. The causal relationship k is positive, the data are not self-contradictory. The necessary condition relationship between EBV VCA IgG and BC is given as $\frac{386+384+15}{798} = 0,983709273..$ Considered in all aspects, the result is statistically significant. In other words, **without** EBV VCA IgG **no** BC (P Value = 0,016158751) .

[93] Cox B, Richardson A, Graham P, Gislefoss RE, Jellum E, Rollag H. Breast cancer, cytomegalovirus and Epstein-Barr virus: a nested case-control study. Br J Cancer. 2010 May 25;102(11):1665-9. doi: 10.1038/sj.bjc.6605675. Epub 2010 Apr 20. PMID: 20407437; PMCID: PMC2883146.

3.6. EBV EBNA-1 IgG and BC: The study of Joshi et al., 2009

Joshi et al. [94] investigated the relationship between EBV and BC.

Table 27. EBV EBNA-1 IgG and BC .

		BC		
		YES	NO	
EBV EBNA-1 IgG	YES	50	27	77
	NO	5	6	11
		55	33	88

STATISTICAL ANALYSIS.

p(IOU)=	0,5
Causal relationship k =	0,1330772827
p (SINE) =	0,9431818182
$\tilde{\chi}^2$ (SINE — B_t) =	0,4545
$\tilde{\chi}^2$ (SINE — $\underline{A}_t$) =	2,2727
p Value right tailed (HGD) =	0,1792
p Value (SINE) =	0,0552341706
RR (nc) =	1,4286
RR (sc) =	1,1111
OR =	2,2222
IOR =	0,0390

The **prevalence** of EBV EBNA-1 IgG in the group of cases is given as $\frac{50}{55} \times 100 = 90,9\%$. The **prevalence** of EBV EBNA-1 IgG in the group of controls is given as $\frac{27}{33} \times 100 = 81,8\%$. The data of the study of Joshi et al. are underestimating the prevalence of EBV EBNA-1 IgG in the population (see table 2, p. 11). The index of independence is p(IOU)= 0,500 (see Barukčić, 2019c, p. 25). The study design of the study of Joshi et al. is very unfair (see table 3, p. 14). Therefore, the data are only of some restricted value. As a consequence, the data of the study of Joshi et al. are biased at least to some extent. In reality, the relationship between EBV EBNA-1 IgG and BC is much stronger than these data do suggest. The causal relationship k is positive, the data are not self-contradictory. The necessary condition relationship between EBV EBNA-1 IgG and BC is given as $\frac{50+27+6}{88} = 0,943181818.$. Considered in all aspects, the result is statistically significant. In other words, **without** EBV EBNA-1 IgG **no** BC (P Value = 0,055234171) .

[94] Joshi D, Quadri M, Gangane N, Joshi R, Gangane N. Association of Epstein Barr virus infection (EBV) with breast cancer in rural Indian women. PLoS One. 2009 Dec 4;4(12):e8180. doi: 10.1371/journal.pone.0008180. PMID: 19997605; PMCID: PMC2782138.

3.7. EBV IgG and BC: The study of Richardson et al., 2004

Richardson et al. [95] investigated the relationship between EBV and BC.

Table 28. EBV VCA IgG and BC .

		BC		
		YES	NO	
EBV VCA IgG	YES	201	162	363
	NO	7	7	14
		208	169	377

STATISTICAL ANALYSIS.

p(IOU)=	0,514588859
Causal relationship k =	0,0204253871
p (SINE) =	0,9814323607
$\tilde{\chi}^2$ (SINE — B_t) =	0,2356
$\tilde{\chi}^2$ (SINE — $\underline{A}_t$) =	3,5000
p Value right tailed (HGD) =	0,4479
p Value (SINE) =	0,0183963226
RR (nc) =	1,1074
RR (sc) =	1,0081
OR =	1,2407
IOR =	0,0036

The **prevalence** of EBV VCA IgG in the group of cases is given as $\frac{201}{208} \times 100 = 96,6\%$. The **prevalence** of EBV VCA IgG in the group of controls is given as $\frac{162}{169} \times 100 = 95,9\%$. The data of the study of Richardson et al. are not underestimating the prevalence of EBV VCA IgG in the population (see table 2, p. 11). The index of independence is p(IOU)= 0,515 (see Barukčić, 2019c, p. 25). The study design of the study of Richardson et al. is highly unfair (see table 3, p. 14). Therefore, the data are only of some restricted value. As a consequence, the data of the study of Richardson et al. are biased at least to some extent. In reality, the relationship between EBV VCA IgG and BC is much stronger than these data do suggest. The causal relationship k is positive, the data are not self-contradictory. The necessary condition relationship between EBV VCA IgG and BC is given as $\frac{201+162+7}{377} = 0,981432361..$ Considered in all aspects, the result is statistically significant. In other words, **without** EBV VCA IgG **no** BC (P Value = 0,018396323) .

[95] Richardson AK, Cox B, McCredie MR, Dite GS, Chang JH, Gertig DM, Southey MC, Giles GG, Hopper JL. Cytomegalovirus, Epstein-Barr virus and risk of breast cancer before age 40 years: a case-control study. Br J Cancer. 2004 Jun 1;90(11):2149-52. doi: 10.1038/sj.bjc.6601822. PMID: 15150559; PMCID: PMC2409506.

3.8. EBV IgG and BC: The study of Richardson et al., 2004 (fair study design)

The data of Richardson et al. [96] were re-investigated under conditions of a fair study design (fictive control group with p(IOU) = 0).

Table 29. EBV VCA IgG and BC .

		BC		
		YES	NO	
EBV VCA IgG	YES	201	4652	4853
	NO	7	200	207
		208	4852	5060

STATISTICAL ANALYSIS.

p(IOU)=	0,000197628
Causal relationship k =	0,0075837418
p (SINE) =	0,9986166008
$\tilde{\chi}^2$ (SINE — B_t) =	0,2356
$\tilde{\chi}^2$ (SINE — $\underline{A}_t$) =	0,2367
p Value right tailed (HGD) =	0,3763
p Value (SINE) =	0,0013824428
RR (nc) =	1,2248
RR (sc) =	1,0079
OR =	1,2345
IOR =	0,0076

The **prevalence** of EBV VCA IgG in the group of cases has not changed and is given as $\frac{201}{208} \times 100 = 96,6\%$. The **prevalence** of EBV VCA IgG in the fictive group of controls has not changed and is given as $\frac{4652}{4852} \times 100 = 95,9\%$. The data of the study of Richardson et al. are not underestimating the prevalence of EBV VCA IgG neither in cases nor in controls (see table 2, p. 11). As a consequence, these data are not biased. In reality, the relationship between EBV VCA IgG and BC is similar to the one which these data do suggest. The index of independence is about p(IOU)= 0,000 (see Barukčić, 2019c, p. 25). The study design of the study of Richardson et al. is not unfair (see table 3, p. 14). Therefore, the data are only of good value. The causal relationship k is positive, the data are not self-contradictory. The necessary condition relationship between EBV VCA IgG and BC is given as $\frac{201+4652+200}{5060} = 0,998616601.$. Considered in all aspects, the result is statistically significant. In other words, **without** EBV VCA IgG **no** BC (P Value = 0,001382443) .

[96] Richardson AK, Cox B, McCredie MR, Dite GS, Chang JH, Gertig DM, Southey MC, Giles GG, Hopper JL. Cytomegalovirus, Epstein-Barr virus and risk of breast cancer before age 40 years: a case-control study. Br J Cancer. 2004 Jun 1;90(11):2149-52. doi: 10.1038/sj.bjc.6601822. PMID: 15150559; PMCID: PMC2409506.

4. Discussion

Can we now draw any conclusions and if so, which ones? Did the methods used by the researchers actually detect or could detect an EBV infection? A very big disadvantage of this study is the lack of any information regarding the sensitivity and specificity of the laboratory methods / kits used by the studies re-analysed. Needless to say, the data published by the studies considered and re-analysed are more or less quite unreliable and the conclusions we draw are only conceivable with the utmost caution. However, as incredible as it may seem, it needs to be considered that besides of a very unfair study design, *the studies were able* to provide convincing evidence of the relationship without an Epstein-Barr virus infection, no human breast cancer. In other words, human breast cancer cannot occur without an EBV infection. One might not believe it, but **without** Epstein-Barr virus infection, **no** human breast cancer. **An Epstein-Barr virus infection is a necessary condition of human breast cancer**. At the same time, it should be borne in mind that other polymerase chain reaction (PCR), in situ hybridization (ISH), immunohistochemistry (IHC) et cetera based studies [97] were able to provide evidence that **an Epstein-Barr virus infection is a sufficient condition of human breast cancer**, too. In other words, **if** EBV infection (of human breast), **then** BC. In the light of all the relevant circumstances, and despite all the difficulties mentioned, we can confidently draw a final conclusion.

5. Conclusion

As outlined before, the following conclusion may be to some extent on shaky ground. Obviously, we cannot longer afford to ignore the facts. As presented by the evidence of this publication, we have many reasons and very strong evidence to be convinced that **Epstein-Barr virus is the cause of human breast cancer**.

Acknowledgments

No funding or any financial support by a third party was received.

6. Patient consent for publication

Not required.

[97] Barukčić, Ilija. (2017). Epstein - Bar virus (EBV) - A cause of human breast cancer. In viXra (Version 1, Number 1, p. 2017). Zenodo. https://doi.org/10.5281/zenodo.4412169

Conflict of interest statement

No conflict of interest to declare.

Erratum

None.

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.

References

Aristotle, of Stageira (384-322 B.C.E). *Metaphysica. Volume VIII. Translated by William David Ross and John Alexander Smith*. The works of Aristotle. At The Clarendon Press, Oxford, 1908. URL http://archive.org/details/worksofaristotle12arisuoft. Archive.org Zenodo.

A. J. Ayer. Negation. *The Journal of Philosophy*, 49(26):797–815, January 1952. doi: 10.2307/2020959. JSTOR.

AL Bailey. The analysis of covariance. *Journal of the American Statistical Association*, 26(176):424–435, 1931.

Monya Baker. 1,500 scientists lift the lid on reproducibility. *Nature*, 533(7604):452–454, 5 2016. ISSN 1476-4687. doi: 10.1038/533452a. PMID: 27225100.

Carl Ludwig von Bar. *Die Lehre vom Kausalzusammenhang im Recht, besonders im Strafrecht*. Verlag von Bernhard Tauchnitz, Leipzig, 1871. URL http://dlib-pr.mpier.mpg.de/m/kleioc/0010/exec/bigpage/%22101657_00000012.gif%22.

Ilija Barukčić. *Die Kausalität*. Wiss.-Verl., Hamburg, 1. aufl. edition, January 1989. ISBN 3-9802216-0-1. ISBN: 978-3-9802216-0-1.

Ilija Barukčić. *Die Kausalität*. Scientia, Wilhelmshaven, 2., völlig überarb. aufl. edition, January 1997. ISBN 3-9802216-4-4. ISBN: 978-3-9802216-4-1.

Ilija Barukčić. *Causality: New statistical methods*. Books on Demand GmbH, Hamburg-Norderstedt, January 2005. ISBN 978-3-8334-3645-1.

Ilija Barukčić. *Causality: New statistical methods*. Books on Demand GmbH, Hamburg-Norderstedt, January 2006a. ISBN 3-8334-3645-X. Deutsche Nationalbibliothek Frankfurt.

Ilija Barukčić. Local hidden variable theorem. *Causation*, 1(1):11–17, Dec. 2006b. URL https://www.causation.eu/index.php/causation/article/view/3.

Ilija Barukčić. Anti Heisenberg-Refutation Of Heisenberg's Uncertainty Relation. In *American Institute of Physics - Conference Proceedings*, volume 1327, pages 322–325, Linnaeus University, Växjö, Sweden, June 14 - 17, 2010, January 2011a. doi: 10.1063/1.3567453. AQT. Web of Science. Full text: American Institute of Physics.

Ilija Barukčić. The Equivalence of Time and Gravitational Field. *Physics Procedia*, 22:56–62, January 2011b. ISSN 18753892. doi: 10.1016/j.phpro.2011.11.008. ICPST 2011. Web of Science. Free full text: Elsevier.

Ilija Barukčić. Anti-Bell - Refutation of Bell's theorem: In: Quantum Theory: Reconsideration of Foundations-6 (QTRF6), Växjö, (Sweden), 11-14 June 2012. In *American Institute of Physics - Conference Proceedings*, volume 1508, pages 354–358, Växjo, Sweden, 2012. American Institute of Physics - Conference Proceedings. doi: 10.1063/1.4773147. QTRF 6. Web of Science. Full text: American Institute of Physics.

Ilija Barukčić. Anti Heisenberg – Refutation of Heisenberg's Uncertainty Principle. *International Journal of Applied Physics and Mathematics*, 4(4):244–250, 2014. IJAPM DOI: 10.7763/IJAPM.2014.V4.292.

Ilija Barukčić. Anti Heisenberg—The End of Heisenberg's Uncertainty Principle. *Journal of Applied Mathematics and Physics*, 04(05):881–887, 2016a. ISSN 2327-4352. JAMP DOI: 10.4236/jamp.2016.45096.

Ilija Barukčić. The Mathematical Formula of the Causal Relationship k. *International Journal of Applied Physics and Mathematics*, 6 (2):45–65, January 2016b. doi: 10.17706/ijapm.2016.6.2.45-65. IJAPM. Free full text: IAP.

Ilija Barukčić. Anti Bohr — Quantum Theory and Causality. *International Journal of Applied Physics and Mathematics*, 7(2):93–111, 2017a. doi: 10.17706/ijapm.2017.7.2.93-111. IJAPM DOI: 10.17706/ijapm.2017.7.2.93-111.

Ilija Barukčić. *Die Kausalität (1989)*. Books on Demand, Hamburg-Norderstedt, reprint edition, 2017b. ISBN 978-3-7448-1595-6. ISBN-13: 9783744815956.

Ilija Barukčić. *Theoriae causalitatis principia mathematica*. Books on Demand, Hamburg-Norderstedt, 2017c. ISBN 978-3-7448-1593-2. ISBN-13: 9783754331347.

Ilija Barukčić. Fusobacterium nucleatum —The Cause of Human Colorectal Cancer. *Journal of Biosciences and Medicines*, 06(03): 31–69, 2018a. ISSN 2327-5081. doi: 10.4236/jbm.2018.63004.

Ilija Barukčić. Human Papillomavirus—The Cause of Human Cervical Cancer. *Journal of Biosciences and Medicines*, 06(04):106–125, 2018b. ISSN 2327-5081. doi: 10.4236/jbm.2018.64009.

Ilija Barukčić. Aristotle's law of contradiction and einstein's special theory of relativity. *Journal of Drug Delivery and Therapeutics*, 9 (22):125–143, 3 2019a. ISSN 2250-1177. doi: 10.22270/jddt.v9i2.2389.

Ilija Barukčić. Index of Independence. *Modern Health Science*, 2(2):1–25, 10 2019b. ISSN 2576-7305. doi: 10.30560/mhs.v2n2p1. URL https://j.ideasspread.org/index.php/mhs/article/view/331. Modern Health Science.

Ilija Barukčić. Index of Unfairness. *Modern Health Science*, 2(1):22, 4 2019c. ISSN 2576-7305, 2576-7291. doi: 10.30560/mhs.v2n1p22. Modern Health Science.

Ilija Barukčić. The P Value of likely extreme events. *International Journal of Current Science Research*, 5(11):1841–1861, 2019d. IJCSR . Free full text: ZENODO.

Ilija Barukčić. Causal relationship k. *International Journal of Mathematics Trends and Technology IJMTT*, 66(10):76–115, 2020a. URL http://www.ijmttjournal.org/archive/ijmtt-v66i10p512. IJMTT.

Ilija Barukčić. Locality and Non locality. *European Journal of Applied Physics*, 2(5):1–13, October 2020b. ISSN 2684-4451. doi: 10.24018/ejphysics.2020.2.5.22. URL https://ej-physics.org/index.php/ejphysics/article/view/22. Free full text: EJAP.

Ilija Barukčić. *N-th index D-dimensional Einstein gravitational field equations. Geometry unchained.*, volume 1. Books on Demand GmbH, Hamburg-Norderstedt, 1 edition, 2020c. ISBN 978-3-7526-4490-6. ISBN-13: 9783752644906 . Free full text (preprint): ZENODO.

Ilija Barukčić. *Zero and infinity. Mathematics without frontiers*. Books on Demand GmbH, Hamburg-Norderstedt, 1 edition, 2020d. ISBN 978-3-7519-1873-2. ISBN-13: 9783751918732.

Ilija Barukčić. Mutually exclusive events. *Causation*, 16(11):5–57, November 2021a. doi: 10.5281/zenodo.5746415. URL https://doi.org/10.5281/zenodo.5746415. Zenodo.

Ilija Barukčić. Index of relationship. *Causation*, 16(8):5–37, April 2021b. doi: 10.5281/zenodo.5163179. URL https://doi.org/10.5281/zenodo.5163179. Zenodo.

Ilija Barukčić. The causal relationship k. *MATEC Web of Conferences*, 336:09032, 2021c. ISSN 2261-236X. doi: 10.1051/matecconf/202133609032. CSCNS2020. Web of Science. Free full text: EDP Sciences.

Ilija Barukčić. The logical content of the risk ratio. *Causation*, 16(4):5–41, February 2021d. doi: 10.5281/zenodo.4679509. Free full text: Zenodo.

Ilija Barukčić. Conditio per quam. *Causation*, 17(3):5–86, March 2022a. doi: 10.5281/zenodo.6369831. URL https://doi.org/10.5281/zenodo.6369831. Zenodo.

Ilija Barukčić. Conditio sine qua non. *Causation*, 17(jan):23–102, 2022b. URL https://doi.org/10.5281/zenodo.5854744. Zenodo.

Ilija Barukčić. Variance of binomial distribution. *Causation*, 17(1):5–22, 1 2022c. URL https://www.causation.eu/index.php/causation/article/view/7.

Ilija Barukčić and Okoh Ufuoma. *Analysis of Switching Resistive Circuits A Method Based on the Unification of Boolean and Ordinary Algebras*. Books on Demand, Hamburg-Norderstedt, first edition edition, 2020. ISBN 978-3-7519-8474-4. ISBN-13: 9783751984744.

Thomas Bayes. LII. An essay towards solving a problem in the doctrine of chances. By the late Rev. Mr. Bayes, FRS communicated by Mr. Price, in a letter to John Canton, AMFR S. *Philosophical transactions of the Royal Society of London*, 53(1):370–418, 1763. The Royal Society London.

Jacobi Bernoulli. *Ars conjectandi, Opus posthumus: Accedit Tractatus de seriebus infinitis ; et epistola Gallice scripta De Ludo Pilae Reticularis*. Impensis Thurnisiorum [Tournes], fratrum, Basileae (Basel, Suisse), January 1713. doi: 10.3931/e-rara-9001. Free full text: e-rara, Zurich, CH.

Alan Birnbaum. On the foundations of statistical inference: Binary experiments. *Annals of Mathematical Statistics*, 32(1):340–341, 1961. jstor.

Hubert M. Blalock. *Causal inferences in nonexperimental research*. Univ. of North Carolina Press, Chapel Hill, NC, 6. printing edition, 1972. ISBN 978-0-8078-0917-4.

Ethan D. Bloch. *Proofs and fundamentals: a first course in abstract mathematics*. Springer, 2nd ed edition, 2011. ISBN 978-1-4419-7126-5.

Niels Bohr. Causality and Complementarity. *Philosophy of Science*, 4(3):289–298, July 1937. ISSN 0031-8248, 1539-767X. doi: 10.1086/286465. URL http://www.informationphilosopher.com/solutions/scientists/bohr/Causality_and_Complementarity.pdf. Informationphilosopher.

George Boole. *An investigation of the laws of thought, on which are founded mathematical theories of logic and probabilities*. New York, Dover, 1854. Free full text: archive.org, San Francisco, CA 94118, USA.

Max Born. Zur Quantenmechanik der Stoßvorgänge. *Zeitschrift für Physik*, 37(12):863–867, December 1926. ISSN 0044-3328. doi: 10.1007/BF01397477. URL https://doi.org/10.1007/BF01397477.

Auguste Bravais. Analyse mathématique sur les probabilités d es erreurs de situation d'un point. *Mémoires Présentées Par Divers Savants À L'Académie Royale Des Sciences De L'Institut De France*, 9:255–332, January 1846.

Bundesanwaltschaft Bundesgerichtshof für Strafsachen. *Entscheidungen des Bundesgerichtshofes*, volume 1 of *Entscheidungen des Bundesgerichtshofes*. Carl Heymanns Verlag, Detmold, 1951. URL https://juris.bundesgerichtshof.de/cgi-bin/rechtsprechung/document.py?Gericht=bgh&Art=en&Datum=2008&Seite=99&nr=43553&pos=2985&anz=3634.

Walter A. Carnielli and João Marcos. Ex contradictione non sequitur quodlibet. *Bulletin of Advanced Reasoning and Knowledge*, 7 (1):89–109, 2001. URL https://www.researchgate.net/publication/236647971_Ex_contradictione_non_sequitur_quodlibet.

K. C. Carter. Koch's postulates in relation to the work of Jacob Henle and Edwin Klebs. *Medical History*, 29(4):353–374, October 1985. ISSN 0025-7273. doi: 10.1017/s0025727300044689.

Roderick M Chisholm. The contrary-to-fact conditional. *Mind*, 55(220):289–307, 1946.

R. J. Cook and D. L. Sackett. The number needed to treat: a clinically useful measure of treatment effect. *BMJ (Clinical research ed.)*, 310(6977):452–454, 2 1995. ISSN 0959-8138. doi: 10.1136/bmj.310.6977.452. PMID: 7873954. Free full text: PMCID: PMC2548824.

J. Cornfield. A method of estimating comparative rates from clinical data; applications to cancer of the lung, breast, and cervix. *Journal of the National Cancer Institute*, 11(6):1269–1275, 6 1951. ISSN 0027-8874. PMID: 14861651.

D. R. Cox. The regression analysis of binary sequences. *Journal of the Royal Statistical Society. Series B (Methodological)*, 20(2): 215–242, 1958. ISSN 0035-9246. JSTOR.

Harald Cramér. *Random variables and probability distributions*. Cambridge University Press, 1937.

Newton C. A. da Costa. On the theory of inconsistent formal systems. *Notre Dame Journal of Formal Logic*, 15(4):497–510, October 1974. ISSN 0029-4527. doi: 10.1305/ndjfl/1093891487.

Newton Carneiro Alfonso da Costa. Nota sobre o conceito de contradição. *Anuário da Sociedade Paranaense de Matemática*, 1(2):6–8, 1958. URL Portuguese.

Augustus De Morgan. *Formal logic: or, the calculus of inference, necessary and probable*. Taylor and Walton, 1847.

A. P. Dempster. Causality and statistics. *Journal of Statistical Planning and Inference*, 25(3):261–278, July 1990. ISSN 0378-3758. doi: 10.1016/0378-3758(90)90076-7. URL http://www.sciencedirect.com/science/article/pii/0378375890900767.

John Donnelly. Creation ex nihilo. In *Proceedings of the American Catholic Philosophical Association*, volume 44, pages 172–184, 1970. DOI: 10.5840/acpaproc19704425 .

Kenny Easwaran. The role of axioms in mathematics. *Erkenntnis*, 68(3):381–391, 2008. DOI: 10.1007/s10670-008-9106-1.

Meister Eckhart. *Meister Eckhart: Die deutschen Werke, Band 1: Predigten. Editor Josef Quint*, volume 2. W.Kohlhammer Verlag, 1986. ISBN: 978-3-17-061210-5.

Arnold Ehrhardt. Creatio ex nihilo. *Studia Theologica - Nordic Journal of Theology*, 4(1):13–43, 1950. doi: 10.1080/00393385008599697. URL https://doi.org/10.1080/00393385008599697. DOI: 10.1080/00393385008599697 .

A. Einstein. Quanten-Mechanik Und Wirklichkeit. *Dialectica*, 2(3-4):320–324, 1948. ISSN 1746-8361. doi: 10.1111/j.1746-8361.1948.tb00704.x. URL https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1746-8361.1948.tb00704.x. Dialectica.

Albert Einstein. Zur Elektrodynamik bewegter Körper. *Annalen der Physik*, 322(10):891–921, 1905. ISSN 1521-3889. doi: https://doi.org/10.1002/andp.19053221004. Wiley Online Library.

Albert Einstein. Kosmologische betrachtungen zur allgemeinen relativitätstheorie. *Sitzungsberichte der Königlich Preußischen Akademie der Wissenschaften (Berlin)*, page 142–152, 1917.

Albert Einstein. Induktion and Deduktion in der Physik. *Berliner Tageblatt and Handelszeitung*, page Suppl. 4, December 1919. URL https://einsteinpapers.press.princeton.edu/vol7-trans/124. Berliner Tageblatt and Handelszeitung.

Ruiz Espejo. Review of Causality: New Statistical Methods, 2nd edn (by Ilija Barukcic; Books on Demand, Norderstedt DE, 2006): 34:1013-1014. *Journal of Applied Statistics*, 34(8):1011–1017, October 2007. doi: 10.1080/02664760701590707. URL http://www.tandfonline.com/doi/abs/10.1080/02664760701590707.

William Feller. *Introduction to Probability Theory and its Applications. Volume I & II.*, volume 1. John Wiley and Sons Inc., 1st edition edition, 1 1950. John Wiley and Sons Inc.

Johann Gottlieb Fichte. *Science of knowledge*. The english and foreign philosophical library. Trübner & Co., London, 1889.

Ronald Aylmer Fisher. On the Interpretation of Chi square from Contingency Tables, and the Calculation of P. *Journal of the Royal Statistical Society*, 85(1):87–94, 1922. ISSN 0952-8385. doi: 10.2307/2340521. JSTOR.

Ronald Aylmer Fisher. The logic of inductive inference. *Journal of the Royal Statistical Society*, 98(1):39–82, 1935. ISSN 0952-8385. doi: 10.2307/2342435. JSTOR.

Ronald Aylmer Fisher. The negative binomial distribution. *Annals of Eugenics*, 11(1):182–187, 1941. ISSN 2050-1439. doi: 10.1111/j.1469-1809.1941.tb02284.x. Wiley Online Library.

Fisher, Ronald Aylmer. XV.—The Correlation between Relatives on the Supposition of Mendelian Inheritance. *Earth and Environmental Science Transactions of The Royal Society of Edinburgh*, 52(2):399–433, 1919. ISSN 2053-5945. doi: 10.1017/S0080456800012163. Royal Society of Edinburgh.

Fisher, Ronald Aylmer. *The genetical theory of natural selection*. At the University Press, 1930. Archive.org.

George Francis FitzGerald. The ether and the earth's atmosphere. *Science (New York, N.Y.)*, 13(328):390, 5 1889. ISSN 0036-8075. doi: 10.1126/science.ns-13.328.390.

Lewis S Ford. An alternative to creatio ex nihilo. *Religious Studies*, 19(2):205–213, 1983. DOI: 10.1017/S0034412500015031 .

Eckart Förster and Yitzhak Y Melamed. *"Omnis determinatio est negatio" – Determination, Negation and Self-Negation in Spinoza, Kant, and Hegel. In: Spinoza and German idealism. Eckart Forster & Yitzhak Y. Melamed (eds.)*. Cambridge University Press, Cambridge [England]; New York, 2012. ISBN 978-1-283-71468-6. URL https://doi.org/10.1017/CBO9781139135139.

Francis Galton. Typical Laws of Heredity. *Nature*, 15(388):492–495, April 1877. ISSN 0028-0836, 1476-4687. doi: 10.1038/015492a0. URL http://www.nature.com/articles/015492a0.

Gauß, Carl Friedrich. *Theoria motus corporum coelestium in sectionibus conicis solem ambientium*. sumtibus Frid. Perthes et I. H. Besser, 1809. e-rara, Zurich, CH.

H. T. Gonin. XIV. The use of factorial moments in the treatment of the hypergeometric distribution and in tests for regression. *The London, Edinburgh, and Dublin Philosophical Magazine and Journal of Science*, 21(139):215–226, January 1936. ISSN 1941-5982. doi: 10.1080/14786443608561573. Taylor and Francis.

Nelson Goodman. The problem of counterfactual conditionals. *The Journal of Philosophy*, 44(5):113–128, 1947.

William Sealy Gosset. The probable error of a mean. *Biometrika*, 6(1):1–25, 1908. ISSN 0006-3444. doi: 1. JSTOR.

William Sealy Gosset. The elimination of spurious correlation due to position in time or space. *Biometrika*, 10(1):179–180, 1914. ISSN 0006-3444. doi: 10.2307/2331746. JSTOR.

C. W. J. Granger. Investigating causal relations by econometric models and cross-spectral methods. *Econometrica*, 37(3):424—-438, 1969. JSTOR.

Major Greenwood and G. Udny Yule. The statistics of anti-typhoid and anti-cholera inoculations, and the interpretation of such statistics in general. *Proceedings of the Royal Society of Medicine*, 8:113–194, 6 1915. ISSN 0035-9157. doi: 10.1177/003591571500801433. PMID: 19978918. Free full text: PMCID: PMC2004181.

J. B. S. Haldane. Karl Pearson, 1857-1957. Being a Centenary Lecture. *Biometrika*, 44(3/4):303–313, 1957. ISSN 0006-3444. doi: 10.2307/2332863. URL https://www.jstor.org/stable/2332863. Biometrika Trust.

John Burdon Sanderson Haldane. The fitting of binomial distributions. *Annals of Eugenics*, 11(1):179–181, 1941. ISSN 2050-1439. doi: 10.1111/j.1469-1809.1941.tb02283.x. Wiley Online Library.

Hansemann, David Paul von. *Ueber das konditionale Denken in der Medizin und seine Bedeutung für die Praxis*. A. Hirschwald, Berlin, 1912. URL https://catalogue.bnf.fr/ark:/12148/cb30574869t.public.

Klaus Hedwig. Negatio negationis: Problemgeschichtliche Aspekte einer Denkstruktur. *Archiv für Begriffsgeschichte*, 24(1):7–33, 1980. ISSN 0003-8946. URL www.jstor.org/stable/24359358.

Hegel, Georg Wilhelm Friedrich. *Wissenschaft der Logik. Erster Band. Erstes Buch*. Johann Leonhard Schrag, Nürnberg, December 1812a. doi: 10.5281/zenodo.5917182. URL https://doi.org/10.5281/zenodo.5917182. Online at: Archive.org Zenodo.

Hegel, Georg Wilhelm Friedrich. *Wissenschaft der Logik. Erster Band. Erstes Buch*. Johann Leonhard Schrag, Nürnberg, December 1812b. doi: 10.5281/zenodo.5917182. URL https://doi.org/10.5281/zenodo.5917182. Online at: Archive.org Zenodo.

Hegel, Georg Wilhelm Friedrich. *Wissenschaft der Logik. Erster Band. Zweites Buch*. Johann Leonhard Schrag, Nürnberg, December 1813. doi: 10.5281/zenodo.5919885. URL https://doi.org/10.5281/zenodo.5919885. Online at: Archive.org Zenodo.

Hegel, Georg Wilhelm Friedrich. *Wissenschaft der Logik. Zweiter Band*. Johann Leonhard Schrag, Nürnberg, December 1816. doi: 10.5281/zenodo.5920022. URL https://doi.org/10.5281/zenodo.5920022. Online at: Archive.org Zenodo.

Hegel, Georg Wilhelm Friedrich. *The Science of Logic. Translated and edited by George Di Giovanni*. Cambridge University Press, Cambridge, USA, 2010. ISBN-13: 978-0-511-78978-6.

Heinemann, Fritz H. The Meaning of Negation. *Proceedings of the Aristotelian Society*, 44:127–152, 1943. ISSN 0066-7374. Oxford University Press.

Heisenberg, Werner Karl. Über den anschaulichen Inhalt der quantentheoretischen Kinematik und Mechanik. *Zeitschrift für Physik*, 43 (3):172–198, March 1927. ISSN 0044-3328. doi: 10.1007/BF01397280. URL https://doi.org/10.1007/BF01397280.

Friedrich Robert Helmert. Über die Wahrscheinlichkeit der Potenzsummen der Beobachtungsfehler und über einige damit im Zusammenhange stehende Fragen. *Zeitschrift für Mathematik und Physik*, 21(3):102–219, 1876.

Friedrich Gustav Jacob Henle. *Von den Miasmen und Contagien und von den miasmatisch-contagiösen Krankheiten*. Verlag von August Hirschwald, Berlin, 1840. URL https://doi.org/10.11588/diglit.15175. University Heidelberg urn:nbn:de:bsz:16-diglit-151756.

Boris Hennig. The Four Causes. *The Journal of Philosophy*, 106(3):137–160, March 2009. doi: 10.5840/jphil200910634.

Hessen, Johannes. *Das Kausalprinzip*. Verlag: Filser, Augsburg, 1928.

Germund Hesslow. Two Notes on the Probabilistic Approach to Causality. *Philosophy of Science*, 43(2):290–292, June 1976. ISSN 0031-8248, 1539-767X. doi: 10.1086/288684. URL https://www.journals.uchicago.edu/doi/10.1086/288684.

Germund Hesslow. Causality and Determinism. *Philosophy of Science*, 48(4):591–605, 1981. ISSN 0031-8248. URL https://www.jstor.org/stable/186838.

Austin Bradford Hill. The environment and disease: association or causation? *Proceedings of the Royal Society of Medicine*, 58: 295–300, January 1965.

Holbach, Paul Henri Thiry Baron de. *Système de la nature, ou des loix du monde physique et du monde moral. Première partie*. Par Jean Baptiste de Mirabaud, Londres, 1770. URL https://doi.org/10.3931/e-rara-14756. Zenodo.

Laurence R. Horn. *A natural history of negation*. University of Chicago Press, Chicago, 1989. ISBN 978-0-226-35337-1. ISBN: 978-0-226-35337-1.

Christiaan Huygens and Frans van Schooten. *De ratiociniis in ludo alae: In: Exercitationum mathematicarum liber primus [- quintus]*. ex officina Johannis Elsevirii, Lugdunum Batavorum (Leiden, The Netherlands), January 1657. doi: 10.3931/e-rara-8813. Free full text: e-rara, Zurich, CH.

Justice Matthews, Mr. Hayes, by next Friend, v. Michigan Central R. Co., 111 U.S. 228, 1884. Argued March 19, 1884. Decided April 7. *U. S. Supreme Court*, 1884. U. S. Supreme Court, 1884.

Michal Kicinski, David A. Springate, and Evangelos Kontopantelis. Publication bias in meta-analyses from the cochrane database of systematic reviews. *Statistics in Medicine*, 34(20):2781–2793, 9 2015. ISSN 1097-0258. doi: 10.1002/sim.6525. PMID: 25988604.

Mirjam J. Knol. Down with odds ratios: risk ratios in cohort studies and randomised clinical trials (article in dutch). *Nederlands Tijdschrift Voor Geneeskunde*, 156(28):A4775, 2012. ISSN 1876-8784. PMID: 22805792.

Anton Friedrich Koch. Die Selbstbeziehung der Negation in Hegels Logik. *Zeitschrift für philosophische Forschung*, 53(1):1–29, 1999. ISSN 0044-3301. URL www.jstor.org/stable/20484868.

Robert Koch. Neue Untersuchungen über die Mikroorganismen bei infektiösen Wundkrankheiten. *Deutsche Medizinische Wochenschrift*, 4(43):531–533, 1878. Zenodo.

Kolmogoroff, Andreĭ Nikolaevich. *Grundbegriffe der Wahrscheinlichkeitsrechnung*. Springer Berlin Heidelberg, Berlin, Heidelberg, January 1933. ISBN 978-3-642-49596-0. Springer.

Kolmogorov, Andreĭ Nikolaevich. *Foundations of the theory of probability. Translated by Nathan Morrison*. Chelsea Publishing Company, 1950. ISBN 978-0-486-82159-7. archive.org, San Francisco, CA 94118, USA.

Korch, Helmut. *Das Problem der Kausalität*. Dt. Verlag der Wissenschaften, Berlin, 1965.

Günter Kröber. Der Konditionalismus und seine Kritik in der sowjetischen Wissenschaft. *Wissenschaftliche Zeitschrift der Karl-Marx Universität Leipzig*, 10(2):137–153, 1961.

Kenneth Kunen. Negation in logic programming. *The Journal of Logic Programming*, 4(4):289–308, December 1987. ISSN 0743-1066. doi: 10.1016/0743-1066(87)90007-0. URL http://www.sciencedirect.com/science/article/pii/0743106687900070.

Harold Langsam. Kant, Hume, and Our Ordinary Concept of Causation. *Philosophy and Phenomenological Research*, 54(3):625, September 1994. ISSN 00318205. doi: 10.2307/2108584. URL https://www.jstor.org/stable/2108584?origin=crossref.

Pierre Simon de LaPlace. *Théorie analytique des probabilités*. Courcier, 1 1812. e-rara, Zurich, CH.

Joseph Larmor. IX. A dynamical theory of the electric and luminiferous medium.— Part III. Relations with material media. *Philosophical Transactions of the Royal Society of London. Series A, Containing Papers of a Mathematical or Physical Character*, 190:205–300, 1 1897. doi: 10.1098/rsta.1897.0020.

Andreas Laupacis, David L. Sackett, and Robin S. Roberts. An assessment of clinically useful measures of the consequences of treatment. *New England Journal of Medicine*, 318(26):1728–1733, 1988. doi: 10.1056/NEJM198806303182605. PMID: 3374545. NEJM.

Gottfried Wilhelm Leibniz. *Oeuvres philosophiques latines & françoises de feu Mr. de Leibnitz*. Chez Jean Schreuder, Amsterdam (NL), 1765. URL https://archive.org/details/oeuvresphilosoph00leibuoft/page/n9.

David Kellogg Lewis. Causation. *The journal of philosophy*, 70(17):556–567, 1974.

Lewis, David Kellogg. *Counterfactuals*. Blackwell, 1973. Blackwell.

Alessandro Liberati, Douglas G. Altman, Jennifer Tetzlaff, Cynthia Mulrow, Peter C. Gøtzsche, John P. A. Ioannidis, Mike Clarke, P. J. Devereaux, Jos Kleijnen, and David Moher. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS medicine*, 6(7):1000100, January 2009. doi: 10.1371/journal.pmed.1000100.

Hendrik Anton Lorentz. De relatieve beweging van de aarde en den aether. *Verslagen der Afdeeling Natuurkunde van de Koninklijke Akademie van Wetenschappen*, 1:74–79, 1892.

Hendrik Antoon Lorentz. Simplified theory of electrical and optical phenomena in moving systems. *Verhandelingen der Koninklijke Akademie van Wetenschappen*, 1:427–442, 1899.

D. Massel and M. K. Cruickshank. The number remaining at risk: an adjunct to the number needed to treat. *The Canadian Journal of Cardiology*, 18(3):254–258, 3 2002. ISSN 0828-282X. PMID: 11907613.

David Moher, Alessandro Liberati, Jennifer Tetzlaff, Douglas G. Altman, and PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the prisma statement. *Annals of Internal Medicine*, 151(4):264–269, W64, 8 2009. ISSN 1539-3704. doi: 10.7326/0003-4819-151-4-200908180-00135.

Abraham de Moivre. *The Doctrine of Chances or a Method of Calculating the Probability of Events in Play. First Edition*. W. Pearson, for the author, London, January 1718. doi: 10.3931/e-rara-10420. Archive.org, USA e-rara, Zurich, CH.

Abraham de Moivre. *The Doctrine of Chances or a Method of Calculating the Probability of Events in Play. Third Edition*. A. Miller, in the Strand, London, January 1756. doi: 10.5281/zenodo.5758598. e-rara, Zurich, CH Zenodo.

Jürgen Neffe. *Einstein: A Biography*. Farrar, Straus and Giroux, New York (USA), 2006.

Russell Newstadt. *Omnis Determinatio est Negatio: A Genealogy and Defense of the Hegelian Conception of Negation*. Loyola University Chicago, Chicago (IL), dissertation edition, 2015. Free full text: Loyola University Chicago, USA.

Jerzy Neyman and Egon Sharpe Pearson. IX. On the problem of the most efficient tests of statistical hypotheses. *Philosophical Transactions of the Royal Society of London. Series A, Containing Papers of a Mathematical or Physical Character*, 231(694–706): 289–337, 2 1933. ISSN 0264-3952, 2053-9258. doi: 10.1098/rsta.1933.0009. The Royal Society, London, GB.

Jean George Pierre Nicod. A reduction in the number of primitive propositions of logic. *Proceedings of the Cambridge Philosophical Society*, 19:32–41, 1917.

Jean George Pierre Nicod. Les relations des valeurs et les relations de sens en logique formelle. *Revue de métaphysique et de morale*, 31:467–480, 1924.

Judea Pearl. *Causality: models, reasoning, and inference*. Cambridge University Press, Cambridge, U.K. ; New York, 2000. ISBN 978-0-521-89560-6.

Karl Pearson. III. Contributions to the Mathematical Theory of Evolution. On the Dissection of Asymmetrical-Frequency Curves. *Philosophical Transactions of the Royal Society of London, Series A*, 185:71–85, 1894. The Royal Society.

Karl Pearson. VII. Mathematical contributions to the theory of evolution.—III. Regression, heredity, and panmixia. *Philosophical Transactions of the Royal Society of London. Series A, Containing Papers of a Mathematical or Physical Character*, 187:253–318, January 1896. doi: 10.1098/rsta.1896.0007. URL https://royalsocietypublishing.org/doi/abs/10.1098/rsta.1896.0007.

Karl Pearson. XV. On certain properties of the hypergeometrical series, and on the fitting of such series to observation polygons in the theory of chance. *The London, Edinburgh, and Dublin Philosophical Magazine and Journal of Science*, 47(285):236–246, January 1899. ISSN 1941-5982. doi: 10.1080/14786449908621253. Taylor and Francis.

Karl Pearson. X. On the criterion that a given system of deviations from the probable in the case of a correlated system of variables is such that it can be reasonably supposed to have arisen from random sampling. *The London, Edinburgh, and Dublin Philosophical Magazine and Journal of Science*, 50(302):157–175, July 1900. ISSN 1941-5982. doi: 10.1080/14786440009463897. Taylor and Francis.

Karl Pearson. III. Mathematical contributions to the theory of evolution. — XII. On a generalised Theory of alternative Inheritance, with special reference to Mendel's laws. *p 66: Standard dev binomial distribution*, 203(359–371):53–86, 1 1904a. doi: 10.1098/rsta.1904.0015. Royal Society.

Karl Pearson. *Mathematical contributions to the theory of evolution. XIII. On the theory of contingency and its relation to association and normal correlation*. Biometric Series I. Dulau and Co., London, January 1904b. Free full text: archive.org, San Francisco, CA 94118, USA.

Karl Pearson. *The Grammar of Science. Third Edition*. Adam and Charles Black, London (GB), 1911. ISBN 978-1-108-07711-8. doi: 10.1017/CBO9781139878548. Free full text: archive.org, San Francisco, CA 94118, USA.

Jules Henri Poincaré. Sur la dynamique de l'électron. *Comptes rendus hebdomadaires des séances de l'Académie des sciences*, 140: 1504–1508, 1905.

Graham Priest. What is so Bad about Contradictions? *The Journal of Philosophy*, 95(8):410–426, 1998. ISSN 0022-362X. doi: 10.2307/2564636. URL https://www.jstor.org/stable/2564636.

Graham Priest, Richard Sylvan, Jean Norman, and A. I. Arruda, editors. *Paraconsistent logic: essays on the inconsistent*. Analytica. Philosophia, München ; Hamden [Conn.], 1989. ISBN 978-3-88405-058-3.

Francisco Miró Quesada, editor. *Heterodox logics and the problem of the unity of logic. In: Non-Classical Logics, Model Theory, and Computability: Proceedings of the Third Latin-American symposium on Mathematical Logic, Campinas, Brazil, July 11-17, 1976. Arruda, A. I., Costa, N. C. A. da, Chuaqui, R. (Eds.).*, volume 89 of *Studies In Logics And The Foundations Of Mathematics*. North-Holland, Amsterdam ; New York : New York, February 1977. ISBN 978-0-7204-0752-5.

Connie Robertson. *The Wordsworth Dictionary of Quotations. Edited by Connie Robertson*. Wordsworth, Ware, Hertfordshire, 1998. ISBN 978-1-85326-751-2. ISBN: 1-85326-489-X.

Josiah Royce. *Negation*, volume 9 of *Encyclopaedia of Religion and Ethics. J. Hastings (ed.)*. Charles Scribner's Sons, New York (USA), 1917. Free full text: archive.org, San Francisco, CA 94118, USA.

Bertrand Russell. *The problems of philosophy*. H. Holt, 1912. archive.org.

Sackett, DL and Deeks, JJ and Altman, DG. Down with odds ratios! *Evidence-Based Med.*, 1:164–166, 1996. *.pdf file DOI: 10.1136/ebm.1996.1.164.

D. A. Sadowsky, A. G. Gilliam, and J. Cornfield. The statistical association between smoking and carcinoma of the lung. *Journal of the National Cancer Institute*, 13(5):1237–1258, 4 1953. ISSN 0027-8874. PMID: 13035448.

Schlick, Friedrich Albert Moritz. Die Kausalität in der gegenwärtigen Physik. *Naturwissenschaften*, 19:145–162, 2 1931. ISSN 0028-1042. doi: 10.1007/BF01516406. Springer.

Schrödinger, Erwin Rudolf Josef Alexander. An undulatory theory of the mechanics of atoms and molecules. *Physical Review*, 28: 1049–1070, Dec 1926. doi: 10.1103/PhysRev.28.1049. URL https://link.aps.org/doi/10.1103/PhysRev.28.1049.

Schrödinger, Erwin Rudolf Josef Alexander. Was ist ein Naturgesetz? *Naturwissenschaften*, 17(1):9–11, January 1929. ISSN 1432-1904. doi: 10.1007/BF01505758. URL https://doi.org/10.1007/BF01505758.

Schrödinger, Erwin Rudolf Josef Alexander. Are there quantum jumps? *British Journal for the Philosophy of Science*, 3(11):233–242, 1952. doi: 10.1093/bjps/III.11.233.

Henry Maurice Sheffer. A set of five independent postulates for boolean algebras, with application to logical constants. *Transactions of the American Mathematical Society*, 14(4):481–488, 1913. ISSN 0002-9947, 1088-6850. doi: 10.1090/S0002-9947-1913-1500960-1. Free full text: archive.org, San Francisco, CA 94118, USA.

E. Sober. Venetian Sea Levels, British Bread Prices, and the Principle of the Common Cause. *The British Journal for the Philosophy of Science*, 52(2):331–346, January 2001. ISSN 0007-0882. DOI: 10.1093/bjps/52.2.331.

J. L. Speranza and Laurence R. Horn. A brief history of negation. *Journal of Applied Logic*, 8(3):277–301, September 2010. ISSN 1570-8683. DOI: 10.1016/j.jal.2010.04.001 ScienceDirect.

Benedictus de Spinoza. *Opera quae supersunt omnia / iterum edenda curavit, praefationes, vitam auctoris, nec non notitias, quae ad historiam scriptorum pertinent*. in bibliopolio academico, June 1674. doi: 10.5281/zenodo.5651174. URL https://doi.org/10.5281/zenodo.5651174. Zenodo.

Wolfgang Spohn. *Eine Theorie der Kausalität*. Fakultät für Philosophie, Wissenschaftstheorie und Statistik. Ludwig-Maximilians-Universität München, 1983. Uni Konstanz.

Patrick Suppes. *A probabilistic theory of causality*. Number Fasc. 24 in Acta philosophica Fennica. North-Holland Pub. Co, Amsterdam, 1970. ISBN 978-0-7204-2404-1.

M. E. Thompson. Ilija Barukčić. Causality. New Statistical Methods. A Book Review. *International Statistical Institute - Short Book Review*, 26(01):6, January 2006. ISI - Short Book Reviews, p. 6.

William Todd. Causes and counterfactuals. In *Analytical Solipsism*, pages 127–149. Springer, 1968.

Tamar Tsopurashvili. Negatio negationis als Paradigma in der Eckhartschen Dialektik. In *Universalità della Ragione. A. Musco (ed.)*, volume II.1, pages 595–602, Palermo, 17-22 settembre 2007, 2012. Luglio.

author Unknown. Kausale und konditionale Weltanschauung. *Nature*, 90(2261):698–699, February 1913. ISSN 1476-4687. doi: 10.1038/090698a0. URL https://www.nature.com/articles/090698a0. Number: 2261 Publisher: Nature Publishing Group.

J. v. Uspensky. *Introduction To Mathematical Probability*. McGraw-Hill Company, New York (USA), 1937. Free full text: archive.org, San Francisco, CA 94118, USA.

Max Verworn. *Kausale und konditionale Weltanschauung*. Verlag von Gustav Fischer, Jena, 1912.

Woldemar Voigt. *Über das Doppler'sche Princip*, volume 8 of *Nachrichten von der Köönigl. Gesellschaft der Wissenschaften und der Georg-Augusts-Universität zu Göttingen*. Dieterichsche Verlags-Buchhandlung, 1887. URL http://archive.org/details/nachrichtenvond04gtgoog. archive.org.

Michael V Wedin. Negation and quantification in aristotle. *History and Philosophy of Logic*, 11(2):131–150, 1990a. Taylor & Francis.

Michael V. Wedin. Negation and quantification in aristotle. *History and Philosophy of Logic*, 11(2):131–150, January 1990b. ISSN 0144-5340. doi: 10.1080/01445349008837163. DOI: 10.1080/01445349008837163.

William Allen Whitworth. *Choice and Chance. With 1000 Exercises*. Deighton, Bell & Co., fifth eidtion edition, 1901. archive.org, San Francisco, CA 94118, USA .

John Woods and Douglas Walton. Post Hoc, Ergo Propter Hoc. *The Review of Metaphysics*, 30(4):569–593, 1977. ISSN 0034-6632. URL https://www.jstor.org/stable/20126985.

Frank Yates. Contingency Tables Involving Small Numbers and the Chi square Test. *Supplement to the Journal of the Royal Statistical Society*, 1(2):217–235, 1934. ISSN 1466-6162. doi: 10.2307/2983604. JSTOR.

Jacob Yerushalmy. Statistical problems in assessing methods of medical diagnosis, with special reference to x-ray techniques. *Public Health Reports (1896-1970)*, pages 1432–1449, 1947. doi: 10.1016/S0140-6736(21)02316-3. JSTOR PMID: 20340527.

George Udny Yule. On the methods of measuring association between two attributes. *Journal of the Royal Statistical Society*, 75(6): 579–652, 1912. ISSN 0952-8385. doi: 10.2307/2340126. JSTOR.

George Udny Yule and Karl Pearson. VII. On the association of attributes in statistics: with illustrations from the material of the childhood society. *Philosophical Transactions of the Royal Society of London. Series A, Containing Papers of a Mathematical or Physical Character*, 194(252–261):257–319, 1 1900. doi: 10.1098/rsta.1900.0019. The Royal Society, London, GB.

Patrick Manuel Zesar. *nihil fit sine causa - Die Kausalität im Spanischen und Portugiesischen: DIPLOMARBEIT. Magister der Philosophie*. Universität Wien, Wien, January 2013. URL http://othes.univie.ac.at/25095/1/2013-01-22_0506065.pdf.

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
[m] https://www.youtube.com/channel/UCwf3w1IngcukIOOjpw8HTwg
[n] https://portal.dnb.de/opac/showNextResultSite?currentResultId=%22Barukcic%22%26any&currentPosition=30