Pancreatic cancer: an infectious (viral) disease?

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Abstract* — *Aim: The rising incidence and the modest therapeutic results of pancreatic cancer is a major medical problem. The aim of this study was to perform a meta-analysis of view case-control studies to stimulate further research in another direction on the etiology of this understudied malignancy.

Methods: The usual bio-statistical methods, publicly available and known, where used.

Results: Helicobacter pylori, smoking and diabetes mellitus do not contribute anything to pancreatic cancer. Chronic pancreatitis appears to be at least one cause of pancreatic cancer, while the cause of chronic pancreatitis has not been investigated. In particular, pancreatic cancer and high blood lipid levels are excluding each other $(p\ Value \equiv 0,0048)$***. Without being married no pancreatic cancer*** $(n = 4821; p\ Value \equiv 0,00166)$***.***

Conclusion: There is some, even if very slight evidence, that pancreatic cancer is a sexually transmitted infectious (viral) disease.

Keywords — ***Pancreatic cancer, Cause, Effect, Causality, Causal relationship.***

I. Introduction

The development of the cancer of the pancreas is a very complex and often silent process. Due to this fact, pancreatic cancer is rarely diagnosed early and is associated with a relatively high death rate that is very close to its incidence rate (see Kamisawa et al., 2016). When it is detected, this cancer is seldom curable. Lastly, pancreatic cancer is a leading cause of cancer death with the poorest prognosis of any major tumour type. Risk factors (see among other: Yadav & Lowenfels, 2013) like cigarette smoking, diabetes mellitus, alcohol consumption, chronic pancreatitis, family histories of cancer in general, genetic susceptibility, lifestyles, physical conditions, and other environmental factors have been examined for a relationship to pancreatic cancer (see among other: Hassan et al., 2007; Keane et al., 2014; Zheng et al., 2016) . Few studies discussed even an associations between viral infections and pancreatic cancer. Hepatitis B (see Hassan et al., 2008) has not been identified for sure as a strong risk factor for pancreatic cancer. In a population-based study of US veterans, Hepatitis C (see El-Serag et al., 2009) has been excluded as a risk factor for pancreatic cancer.
However, to our knowledge, no research has been successful to determine the cause or a cause of pancreatic cancer.

II. Material and Methods

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

A. Material

Search Strategy

A literature search was conducted in the electronic database PubMed. The following keywords and terms relevant to the topic were considered: ‘marital status‘and ‘pancreatic cancer ‘. No restriction was placed on language. According to this criteria, a total of one study with at least an abstract written in English was identified primarily from the database. Studies with data access barriers were excluded from the systematic review. Finally, after further screening, it was possible to identify only two studies (see Bo et al., 2019; Wynder et al., 1986) which provided appropriate data on the marital status and pancreatic cancer which were eligible for the systematic review. The study of Baine et al. (see Baine et al., 2011) offered among other an undifferentiated and inappropriate definition of the marital status and has not been considered for a reanalysis. The data of Hassan et al. (see Hassan et al.,

2008) have not been use because the data are self-contradictory in this respect.

Inclusion and Exclusion Criteria
Original quantitative and qualitative studies published in peer-reviewed and in non peer-reviewed journals were formally considered for a review. Studies were required to provide at least the following baseline characteristics of cases with pancreatic cancer and control subjects about the factors and outcomes analysed: marital status, high blood lipid levels, diabetes mellitus, pancreatitis, smoking, helicobacter pylori.
Data of studies with an p(IOU) > 0,30 ((Zheng et al., 2016)) and with an p(IOI) > 0,30 where treated as biased and where not considered for a review.

Study Selection
The design of this review followed as much as possible the Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) statement (Liberati et al., 2009; Moher et al., 2009). However, as with all research, the value of a systematic review depends on the quality of data analysed and equally of the quality of the statistical methods used too.

Data Extraction
The reviewer extracted data on inclusion and exclusion criteria reported of each included trial. The data were stored in Microsoft®Excel®format.

B. Methods

Processes or events of objective reality, as we ordinarily think of it, cannot be predicted all the time with certainty in advance under any circumstances. Sometimes, events or outcomes occur haphazardly or by chance. However, even if a single event may sometimes be unpredictably, the set of all the possible outcomes is sometimes known. The following methods are described for discrete random variables. The same methods for continuous random variables can be found in literature (Barukčić, 1997, 2019a).

Statistical Analysis
The data were analysed by the methods provided by Microsoft®Excel®for Mac®version 16.2 (181208) software (©2018, Microsoft GmbH, Munich, Germany) and the methods described in this publication. The level of significance was set throughout this publication at α = .05.

Definition 2.1 (**Sample Space, Events, Probability**)**.**

Let ${}_{R}X_{t}$ denote the sample space of an experiment, the set of all the possible outcomes or states at a certain (period of) time or Bernoulli trial t. Let ${}_{0}x_{t}$ denote a single event, a subset of the sample space. Let $p({}_{0}x_{t} = {}_{R}X_{t})$ denote the probability of an event. It is

$$ {}_{R}X_{t} \equiv \{{}_{0}x_{t}, {}_{1}x_{t}, ...\} \tag{1} $$

Definition 2.2 (**Two by two table of Bernoulli random variables**)**.**

Karl Pearson was the first to introduce the notion of a two by two or contingency (Pearson, 1904) table in 1904. A contingency table is an appropriate theoretical model for studying the relationships between two *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 Bernoulli distributed random variable A_t denote a risk factor, a condition or 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 the case of +0/+1 distributed Bernoulli random variables it is

$$ \begin{aligned} E(A_t) &\equiv A_t \times p(A_t) \\ &\equiv p(a_t) + p(b_t) \\ &\equiv (+0+1) \times p(A_t) \\ &\equiv p(A_t) \end{aligned} \tag{2} $$

Let a Bernoulli distributed random variable B_t denote an outcome, a conditioned event or an effect and occur or exist et cetera with the probability $p(B_t)$ at the Bernoulli trial (period of time) t. Let $E(B_t)$ denote the expectation

value of B_t. It is

$$\begin{aligned} E\left(B_t\right) &\equiv B_t \times p\left(B_t\right) \\ &\equiv p\left(a_t\right) + p\left(c_t\right) \\ &\equiv (+0+1) \times p\left(B_t\right) \\ &\equiv p\left(B_t\right) \end{aligned} \tag{3}$$

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

$$\begin{aligned} E\left(a_t\right) &\equiv E\left(A_t \cap B_t\right) \\ &\equiv \left(A_t \times B_t\right) \times p(A_t \cap B_t) \\ &\equiv p(A_t \cap B_t) \\ &\equiv p\left(a_t\right) \end{aligned} \tag{4}$$

Let $p(b_t)= p(A_t \cap \neg B_t)$ 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

$$\begin{aligned} E\left(b_t\right) &\equiv E\left(A_t \cap \neg B_t\right) \\ &\equiv \left(A_t \times \neg B_t\right) \times p(A_t \cap \neg B_t) \\ &\equiv p(A_t \cap \neg B_t) \\ &\equiv p\left(b_t\right) \end{aligned} \tag{5}$$

Let $p(c_t)= p(\neg A_t \cap B_t)$ 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

$$\begin{aligned} E\left(c_t\right) &\equiv E\left(\neg A_t \cap B_t\right) \\ &\equiv \left(\neg A_t \times B_t\right) \times p(\neg A_t \cap B_t) \\ &\equiv p(\neg A_t \cap B_t) \\ &\equiv p\left(c_t\right) \end{aligned} \tag{6}$$

Let $p(d_t)= p(\neg A_t \cap \neg B_t)$ 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

$$\begin{aligned} E\left(d_t\right) &\equiv E\left(\neg A_t \cap \neg B_t\right) \\ &\equiv \left(\neg A_t \times \neg B_t\right) \times p(\neg A_t \cap \neg B_t) \\ &\equiv p(\neg A_t \cap \neg B_t) \\ &\equiv p\left(d_t\right) \end{aligned} \tag{7}$$

In general, it is

$$p\left(a_t\right) + p\left(b_t\right) + p\left(c_t\right) + p\left(d_t\right) \equiv +1 \tag{8}$$

Table 1 provides an overview of the definitions above.

		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

Tabelle 1: Bernoulli random variables

Definition 2.3 (Two by two table of Binomial random variables).

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

$$\begin{aligned} A &= N \times E\left(A_{\mathrm{t}}\right) \\ &\equiv N \times \left(A_{\mathrm{t}} \times p\left(A_{\mathrm{t}}\right)\right) \\ &\equiv N \times \left(p\left(a_{\mathrm{t}}\right) + p\left(b_{\mathrm{t}}\right)\right) \\ &\equiv N \times p\left(A_{\mathrm{t}}\right) \end{aligned} \tag{9}$$

and

$$\begin{aligned} B &= N \times E\left(B_{\mathrm{t}}\right) \\ &\equiv N \times \left(B_{\mathrm{t}} \times p\left(B_{\mathrm{t}}\right)\right) \\ &\equiv N \times \left(p\left(a_{\mathrm{t}}\right) + p\left(c_{\mathrm{t}}\right)\right) \\ &\equiv N \times p\left(B_{\mathrm{t}}\right) \end{aligned} \tag{10}$$

where N denotes the population size. Furthermore, it is

$$a \equiv N \times \left(E\left(a_{\mathrm{t}}\right)\right) \equiv N \times \left(p\left(a_{\mathrm{t}}\right)\right) \tag{11}$$

and

$$b \equiv N \times \left(E\left(b_{\mathrm{t}}\right)\right) \equiv N \times \left(p\left(b_{\mathrm{t}}\right)\right) \tag{12}$$

and

$$c \equiv N \times \left(E\left(c_{\mathrm{t}}\right)\right) \equiv N \times \left(p\left(c_{\mathrm{t}}\right)\right) \tag{13}$$

and

$$d \equiv N \times \left(E\left(d_{\mathrm{t}}\right)\right) \equiv N \times \left(p\left(d_{\mathrm{t}}\right)\right) \tag{14}$$

Furthermore, in general, it is

$$\begin{aligned} A &\equiv a + b \\ \underline{A} &\equiv c + d \\ B &\equiv a + c \\ \underline{B} &\equiv b + d \end{aligned} \tag{15}$$

and

$$\begin{aligned} N &\equiv a + b + c + d \\ &\equiv A + \underline{A} \\ &\equiv B + \underline{B} \end{aligned} \tag{16}$$

The table 2 may provide a principal overview of the definitions of the relationship between two Binomial random variables used in the following of this publication.

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

Tabelle 2: Binomial random variables

Definition 2.4 (Index Of Unfairness).

The the quality of the data published may depend on study design too. systematic reviews and meta-analyses. Therefore, it is appropriate to quantify possible publication bias due to study design. The index of unfairness (IOU) is defined (see Barukčić, 2019c) as

$$\begin{aligned} p\left(IOU\right) &\equiv Absolute\left(\left(\frac{A+B}{N}\right) - 1\right) \\ &\equiv Absolute\left(\left(\frac{\underline{A}+\underline{B}}{N}\right) - 1\right) \end{aligned} \tag{17}$$

Definition 2.5 (**Index Of Independence**)**.**

Publication bias due to study design cannot be excluded completely. The index of independence (IOI) is of use in this context and defined (see Barukčić, 2019b) as

$$\begin{aligned} p\left(IOI\right) &\equiv Absolute\left(\left(\frac{A+\underline{B}}{N}\right)-1\right) \\ &\equiv Absolute\left(\left(\frac{\underline{A}+B}{N}\right)-1\right) \end{aligned} \tag{18}$$

Lemma 2.1 (Placebo controlled trials.)**.** *A well-conducted study with a good study design is of general importance. Especially placebo-controlled clinical trials are more or less standard for clinical investigations of new drugs. Similar patients are allocated (blindly, randomly et cetera) to an experimental group (A) that receives a* ***verum*** *and a control group (*$\underline{A}$*) that receives a* ***placebo****. With respect to study design, many times investigators ensure that* $A \equiv \underline{A}$*. Under these circumstances, the study design demands too, that*

$$p\left(IOU\right) \equiv p\left(IOI\right) \tag{19}$$

Direct proof. A study design of a study may be grounded on

$$A \equiv \underline{A} \tag{20}$$

Adding B, it is

$$A + B \equiv \underline{A} + B \tag{21}$$

Dividing by N, we obtain

$$\frac{A+B}{N} \equiv \frac{\underline{A}+B}{N} \tag{22}$$

Rearranging, it is

$$\frac{A+B}{N} - 1 \equiv \frac{\underline{A}+B}{N} - 1 \tag{23}$$

Taking the absolute, it is

$$Absolute\left(\left(\frac{A+B}{N}\right)-1\right) \equiv Absolute\left(\left(\frac{\underline{A}+B}{N}\right)-1\right) \tag{24}$$

and finally

$$p\left(IOU\right) \equiv p\left(IOI\right) \tag{25}$$

□

However, sample size calculation is an important part of conducting an epidemiological, clinical or other study, and, ideally, samples of studies grounded on $p\left(IOU\right) \equiv p\left(IOI\right)$ should not be too excessive, otherwise systematic bias is probable.

Definition 2.6 (**Independence**)**.**

Historically, logic and probability theory which by time derived from the former are two of the main pillars in the modern study of human reasoning. At first sight, combining logic and probability theory in the same mathematical framework, as done in this publication, might look a little bit strange because probability theory deals more or less with uncertainties whereas logic as such is concerned with absolutely certain inferences or truths. In this context, it is important to note that we will steer clear of the scientific debate over the exact nature and the meaning of probability. However, it is possible to treat **the probability of an event as the truth value of probability theory**. Thus far and in contrast to Fuzzy logic and other trials of non-classical logic, such an approach opens the strategic possibility to develop a logically consistent multi-valued logic. In this context, the concept of independence is of fundamental (Kolmogoroff, 1933) importance in (natural) sciences as such and as old as human mankind itself. The first documented mathematical approach to the concept of independence can be ascribed preliminary to the French mathematician and equally a friend of Isaac Newton (1642 - 1726, the Julian calendar), Abraham de Moivre (1667 – 1754). Abraham de Moivre demands the following: " *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 connected together as that the Probability of either's happening is altered by the happening of the other . . . therefore, those two Events*

being independent, the Probability of their both happening will be $\frac{1}{13} \times \frac{1}{13} \equiv \frac{1}{169}$ "(see Moivre, 1718, p. 6/7). The tremendous improvement of the concept of independence is undoubtedly due to the contributions of many scientists. Andrei Nikolajewitsch Kolmogorow (1903-1987), a Russian mathematician and one of the most important mathematicians of the 20th century mathematics, elaborates on the meaning of concept of independence too. "*The concept of mutual independence of two or more experiments holds, in a certain sense, a central position in the theory of probability . . . In consequence, one of the most important problems in the philosophy of the natural sciences is . . . to make precise the premises which would make it possible to regard any given real events as independent.*"(see Kolmogorov, 1956, p. 8/9). In fact, it is insightful to recall Einstein's theoretical approach to the concept of independence before the mind's eye. "*Ohne die Annahme einer . . . Unabhängigkeit der . . . Dinge voneinander . . . wäre physikalisches Denken . . . nicht möglich.*"(Einstein, 1948). In other words, the existence or the occurrence of an event A_t at the Bernoulli trial t need not but can be independent of the existence or of the occurrence of another event B_t *at the same* Bernoulli trial t. Mathematically, independence (Kolmogoroff, 1933; Moivre, 1718) in terms of probability theory is defined at the same (period of) time t (i. e. Bernoulli trial t) as

$$p\left(A_t \cap B_t\right) \equiv p\left(A_t\right) \times p\left(B_t\right) \tag{26}$$

In a narrower sense, the conditio sine qua non relationship concerns itself at the end only with the case whether the presence of an event A_t (condition) enables or guarantees the presence of another event B_t (conditioned). As a result of these thoughts, another question worth asking concerns the relationship between the independence of an event A_t (a condition) and another event B_t (conditioned) and the necessary condition relationship. To be confronted with the danger of bias and equally with the burden of inappropriate conclusions drawn, another fundamental question at this stage is whether is it possible that an event A_t (a condition) is a necessary condition of event B_t (conditioned) even under circumstances where the event A_t (a condition) (a necessary condition) is independent of an event B_t (conditioned)? This question is already answered more or less to the negative (Barukčić, 2018e). 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 a dependence. Thus far, **data which provide evidence of a significant conditio sine qua non relationship between two events like A_t and B_t and equally support the hypothesis that A_t and B_t are independent of each other are more or less self-contradictory and of very restricted or of none value for further analysis**. In fact, if the opposite view would be taken as plausible, contradictions are more or less inescapable.

Definition 2.7 (**Dependence**)**.**

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

$$p\left(\underbrace{A_t \cap B_t \cap C_t \cap \ldots}_{n}\right) \equiv \sqrt[n]{\underbrace{p\left(A_t\right) \times p\left(B_t\right) \times p\left(C_t\right) \times \ldots}_{n}} \tag{27}$$

Definition 2.8 (**Exclusion relationship [*EXCL*]**)**.**

Mathematically, the exclusion (EXCL) relationship, denoted by $p(A_t \mid B_t)$ in terms of probability theory, is defined as

$$\begin{aligned} p\left(A_t \mid B_t\right) &\equiv p\left(b_t\right) + p\left(c_t\right) + p\left(d_t\right) \\ &\equiv \frac{N \times \left(p\left(b_t\right) + p\left(c_t\right) + p\left(d_t\right)\right)}{N} \\ &\equiv \frac{b+c+d}{N} \\ &\equiv 1 - \left(p\left(A_t \cap B_t\right) \equiv 0\right) \\ &\equiv 1 - \left(p\left(a_t\right) \equiv 0\right) \\ &\equiv \left(p\left(A_t \rightarrow \neg B_t\right)\right) \cap \left(p\left(B_t \rightarrow \neg A_t\right)\right) \\ &\equiv +1 \end{aligned} \tag{28}$$

Conjunction, disjunction, and negation are one of the simplest logical operators. To some extent, exclusion is determined by the negation of a conjunction and can be expressed equivalently in terms of a conditio per quam relationship (definition 2.22) as $p\left(A_t \mid B_t\right) \equiv \left(p\left(A_t \rightarrow \neg B_t\right)\right) \cap \left(p\left(B_t \rightarrow \neg A_t\right)\right) \equiv +1$. In spoken English, **if A_t then ¬ B_t and equally vice versa. If B_t then ¬ A_t** . Table 3 demonstrates the theoretical distribution of an exclusion relationship in terms of a sufficient condition as if A_t then ¬ B_t.

Tabelle 3: Exclusion and sufficient condition I.

		Conditioned B_t		
		NO	YES	
Condition A_t	YES	1	0	A_t
	NO	1	1	$\underline{A_t}$
		$\underline{B_t}$	B_t	1

Table 4 demonstrates the theoretical distribution of an exclusion relationship in terms of a sufficient condition as if B_t then $\neg A_t$.

Tabelle 4: Exclusion and sufficient condition I.

		Conditioned A_t		
		NO	YES	
Condition B_t	YES	1	0	B_t
	NO	1	1	$\underline{B_t}$
		$\underline{A_t}$	A_t	1

Furthermore, consider, for example, that the two events **being a male human being** (A_t = TRUE) and equally **being a pregnant human being** (B_t = TRUE) are excluding each other at the same Bernoulli trial t. Mathematically, let $p(a_t) \equiv p((A_t = \text{TRUE}) \cap (B_t = \text{TRUE}))$ denote the joint probability distribution function of an event A_t and an event B_t. One determining feature of an exclusion relationship is the fact that $p(a_t) \equiv p((A_t = \text{TRUE}) \cap (B_t = \text{TRUE})) \equiv 0$. In other words, in case of an exclusion relationship it is not possible to observe an event A_t and at the same (period of) time or Bernoulli trial t an event B_t. Table 5 provide us with an overview of this example and equally one possible theoretical distribution of an exclusion relationship. Examinations of the protective effects and long-term benefits of commonly used statin therapy in both primary and secondary prevention of cardiovascular disease should be able to provide clear evidence of an exclusion relationship between statin therapy and death due to any (including cardiovascular) cause (Barukčić, 2019e).

		Conditioned (pregnant) B_t		
		TRUE	FALSE	
Condition (male)	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

Tabelle 5: A_t excludes B_t and vice versa.

Definition 2.9 (**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 (Barukčić, 2018b, 2018c) with degree of freedom (d. f.) of d. f. = 1 is calculated as

$$\begin{aligned} \tilde{\chi}^2_{\text{Calculated}}\left((A_t \mid B_t) \mid A\right) &\equiv \frac{(b-(a+b))^2}{A} + \frac{((c+d)-\underline{A})^2}{\underline{A}} \\ &\equiv \frac{a^2}{A} + 0 \\ &\equiv \frac{a^2}{A} \end{aligned} \tag{29}$$

or equally as

$$\begin{aligned}\tilde{\chi}^{2}{}_{\text{Calculated}}\left(\left(A_{\text{t}} \mid B_{\text{t}}\right) \mid B\right) &\equiv \frac{\left(c-(a+c)\right)^{2}}{B}+ \\ &\quad \frac{\left((b+d)-\underline{B}\right)^{2}}{\underline{B}} \\ &\equiv \frac{a^{2}}{B}+0 \\ &\equiv \frac{a^{2}}{B}\end{aligned} \tag{30}$$

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 to be accepted. Yate's (Yates, 1934) continuity correction has not been used under these circumstances.

Definition 2.10 (The left-tailed p Value of an exclusion relationship).

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

$$\begin{aligned}pValue_{\text{lt}}\left(A_{\text{t}} \mid B_{\text{t}}\right) &\equiv 1-e^{-(1-p(A_{\text{t}}|B_{\text{t}}))} \\ &\equiv 1-e^{-(a/N)}\end{aligned} \tag{31}$$

A low p-value may provide some evidence of statistical significance. Table 6 demonstrates another example of the distribution of an exclusion relationship.

Tabelle 6: Exclusion relationship.

		Conditioned B_t		
		YES	NO	
Condition A_t	YES	0	1	1
	NO	1	1	2
		1	2	3

Definition 2.11 (Either A_t or B_t conditions [*NEQV*]).

Mathematically, an either A_t or B_t condition relationship (NEQV), denoted by $p(A_t >-< B_t)$ in terms of probability theory, is defined as

$$\begin{aligned}p\left(A_{\text{t}} >-< B_{\text{t}}\right) &\equiv p\left(b_{\text{t}}\right)+p\left(c_{\text{t}}\right) \\ &\equiv \frac{N \times \left(p\left(b_{\text{t}}\right)+p\left(c_{\text{t}}\right)\right)}{N} \\ &\equiv \frac{b+c}{N} \\ &\equiv +1\end{aligned} \tag{32}$$

Definition 2.12 (The $\tilde{\chi}^{2}$ goodness of fit test of an either or condition relationship).

An either or condition relationship $p(A_t >-< B_t)$ 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 (Barukčić, 2018b, 2018c) with degree of freedom (d. f.) of d. f. = 1 is calculated as

$$\begin{aligned}\tilde{\chi}^{2}{}_{\text{Calculated}}\left(\left(A_{\text{t}} >-< B_{\text{t}}\right) \mid A\right) &\equiv \frac{\left(b-(a+b)\right)^{2}}{A}+ \\ &\quad \frac{c-\left((c+d)\right)^{2}}{\underline{A}} \\ &\equiv \frac{a^{2}}{A}+\frac{d^{2}}{\underline{A}}\end{aligned} \tag{33}$$

or equally as

$$\begin{aligned}\tilde{\chi}^2{}_{\text{Calculated}}\left((A_{\text{t}} > - < B_{\text{t}}) \mid B\right) &\equiv \frac{\left(c-(a+c)\right)^2}{B} + \\ &\quad \frac{b-\left((b+d)\right)^2}{\underline{B}} \\ &\equiv \frac{a^2}{B} + \frac{d^2}{\underline{B}}\end{aligned} \tag{34}$$

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

Definition 2.13 (The left-tailed p Value of an either or condition relationship).

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

$$\begin{aligned}pValue_{\text{lt}}\left(A_{\text{t}} > - < B_{\text{t}}\right) &\equiv 1 - e^{-(1-p(A_{\text{t}}>-<B_{\text{t}}))} \\ &\equiv 1 - e^{-((a+d)/N)}\end{aligned} \tag{35}$$

In this context, a low p-value indicates again a statistical significance. Table 7 provides an illustration of the theoretical distribution of an either A_t or B_t relationship.

Tabelle 7: 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

Definition 2.14 (Neither A_t nor B_t conditions [*NOR*]).

Mathematically, a neither A_t nor B_t condition relationship (NOR), denoted by $p(A_t \uparrow B_t)$ in terms of probability theory, is defined as

$$\begin{aligned}p\left(A_{\text{t}} \uparrow B_{\text{t}}\right) &\equiv p\left(d_{\text{t}}\right) \\ &\equiv \frac{N \times \left(p\left(d_{\text{t}}\right)\right)}{N} \\ &\equiv \frac{d}{N} \\ &\equiv +1\end{aligned} \tag{36}$$

Definition 2.15 (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 $p(A_t \uparrow B_t)$ 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 (Barukčić, 2018b, 2018c) with degree of freedom (d. f.) of d. f. = 1 may be calculated as

$$\begin{aligned}\tilde{\chi}^2{}_{\text{Calculated}}\left((A_{\text{t}} \uparrow B_{\text{t}}) \mid A\right) &\equiv \frac{\left(d-(c+d)\right)^2}{\underline{A}} + \\ &\quad \frac{\left((a+b)-A\right)^2}{A} \\ &\equiv \frac{c^2}{\underline{A}} + 0\end{aligned} \tag{37}$$

or equally as

$$\begin{aligned}\tilde{\chi}^2{}_{\text{Calculated}}\left((A_{\text{t}} \uparrow B_{\text{t}}) \mid B\right) &\equiv \frac{\left(d-(b+d)\right)^2}{\underline{B}} + \\ &\quad \frac{\left((a+c)-B\right)^2}{B} \\ &\equiv \frac{b^2}{\underline{B}} + 0\end{aligned} \tag{38}$$

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

Definition 2.16 (**The left-tailed p Value of a neither A_t nor B_t condition relationship**).

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

$$\begin{aligned} pValue_{\text{lt}}\left(A_t \uparrow B_t\right) &\equiv 1 - e^{-(1-p(A_t \uparrow B_t))} \\ &\equiv 1 - e^{-p(A_t \cup B_t)} \\ &\equiv 1 - e^{-((a+b+c)/N)} \end{aligned} \tag{39}$$

where $\cup$ may denote disjunction or logical or. In this context, a low p-value indicates again a statistical significance. Table 8 provides an illustration of the theoretical distribution of a neither A_t nor B_t relationship.

Tabelle 8: Neither A_t nor B_t relationship.

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

Definition 2.17 (**Necessary condition [*Conditio sine qua non*]**).

Scientific knowledge and objective reality are deeply interrelated. As mentioned at the start of the article, the specification of necessary conditions has traditionally been part of the philosopher's investigations of different phenomena. Behind the need of a detailed evidence it is justified to consider that philosophy as such has certainly not **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 selfenclosed unit. Seemingly **the law's concept of causation** justifies to say few words on this subject, to put some light on some questions. Are there any criteria in law for deciding whether one action or an event A_t has caused another (generally harmful) event B_t? What are these criteria? May causation in legal contexts differ from causation outside the law, for example, in science or in our everyday life and to what extent? Under which circumstances is it justified to tolerate such differences as may be found to exist? To understand just what is the law's concept of causation it is useful to know how the highest court of states is dealing with causation. In the case *Hayes v. Michigan Central R. Co., 111 U.S. 228*, the U.S. Supreme Court defined 1884 conditio sine qua non as follows: "... **causa sine qua non – a cause which, if it had not existed, the injury would not have taken place**". (Justice Matthews, 1884) The German Bundesgerichtshof für Strafsachen stressed once again the importance of conditio sine qua non relationship in his decision by defining the following: "**Ursache eines strafrechtlich bedeutsamen Erfolges jede Bedingung, die nicht hinweggedacht werden kann, ohne daß der Erfolg entfiele**"(Bundesgerichtshof für Strafsachen, 1951) Another lawyer elaborated on the basic issue of **identity and difference between cause and condition**. Von Bar was writing: "Die erste Voraussetzung, welche erforderlich ist, damit eine Erscheinung als die Ursache einer anderen bezeichnet werden könne, ist, daß jene eine der Bedingungen dieser sein. Würde die zweite Erscheinung auch dann eingetreten sein, wenn die erste nicht vorhanden war, so ist sie in keinem Falle Bedingung und noch weniger Ursache. Wo immer ein Kausalzusammenhang behauptet wird, da muß er wenigstens diese Probe aushalten ... **Jede Ursache ist nothwendig auch eine Bedingung eines Ereignisses; aber nicht jede Bedingung ist Ursache zu nennen**."(Bar, 1871) Von Bar's position translated into English: *The first requirement, which is required, thus that something could be called as the cause of another, is that the one has to be one of the conditions of the other. If the second something had occurred even if the first one did not exist, so it is by no means a condition and still less a cause. Wherever a causal relationship is claimed, the same must at least withstand this test... Every cause is necessarily also a condition of an event too; but not every condition is cause too.* Thus far, let us consider among other the following in order to specify necessary conditions from another, probabilistic point of view. An event (i. e. A_t) which is a necessary condition of another event or outcome (i.e. B_t) must be given, must be present for a conditioned, for an event or for an outcome B_t to occur. A necessary condition (i. e. A_t) is a requirement which must be fulfilled **at every single Bernoulli trial t**, in order for a conditioned or an outcome (i.e. B_t) to occur but it alone does not determine the occurrence of an event. In other words, if a necessary condition (i. e. A_t) is given, an outcome (i.e. B_t) need not to occur. In contrast to a necessary condition, a 'sufficient'condition is the one

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

$$\begin{aligned} p\left(A_t \leftarrow B_t\right) &\equiv p\left(a_t\right) + p\left(b_t\right) + p\left(d_t\right) \\ &\equiv \frac{N \times \left(p\left(a_t\right) + p\left(b_t\right) + p\left(d_t\right)\right)}{N} \\ &\equiv \frac{a+b+d}{N} \\ &\equiv +1 \end{aligned} \tag{40}$$

Table 9 provides an overview of the definition of the 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

Tabelle 9: Necessary condition.

Definition 2.18 (The $\tilde{\chi}^2$ goodness of fit test of a necessary condition relationship).

The data as obtained by investigations can vary extremely across studies as well as among and within individuals. Some (experimental) studies may support a hypothesis of a conditio sine qua non relationship between two factors while other may fail on the same matter. An appropriate study design is of essential importance for a successful execution of research. However, each design has its own strengths and weaknesses, and the data achieved need not to guarantee to arrive at correct conclusions. Besides of all, under some known circumstances, testing hypothesis about the conditio sine qua non relationship $p(A_t \leftarrow B_t)$ is possible by the chi-square distribution (also chi-squared or $\tilde{\chi}^2$-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 (Barukčić, 2018b, 2018c) with degree of freedom (d. f.) of d. f. = 1 is calculated as

$$\begin{aligned} {\tilde{\chi}^2}_{\text{Calculated}}\left(A_t \leftarrow B_t \mid B\right) &\equiv \frac{\left(a-\left(a+c\right)\right)^2}{B} + \\ &\quad \frac{\left(\left(b+d\right)-\underline{B}\right)^2}{\underline{B}} \\ &\equiv \frac{c^2}{B} + 0 \\ &\equiv \frac{c^2}{B} \end{aligned} \tag{41}$$

or equally as

$$\begin{aligned}\tilde{\chi}^{2}{}_{\text{Calculated}}\left(A_{\text{t}} \leftarrow B_{\text{t}} \mid \underline{A}\right) &\equiv \frac{\left(d-(c+d)\right)^{2}}{\underline{A}}+ \\ &\quad \frac{\left((a+b)-A\right)^{2}}{A} \\ &\equiv \frac{c^{2}}{\underline{A}}+0 \\ &\equiv \frac{c^{2}}{\underline{A}}\end{aligned} \tag{42}$$

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.

Definition 2.19 (**The expected Chi-Square value of a cell**).

Chi-square is a statistical test commonly used to compare observed data with data we would expect to obtain according to a specific hypothesis. Historically, the chi-square distribution (also chi-squared or $\tilde{\chi}^{2}$-distribution), first described by the German statistician Friedrich Robert Helmert (Helmert, 1876) was rediscovered later by Karl Pearson (Pearson, 1900) in the context of a $\tilde{\chi}^{2}$ goodness of fit test. One of the assumptions of the Chi-square test is not that the observed value in each cell is greater than 5 but that the expected value in each cell is greater than 5. The expected Chi-Square value of **the cell a** of the table 10 is calculated as follows:

$$E\left(a\right) \equiv \frac{\left(A \times B\right)}{N} \tag{43}$$

In other words, for each cell (i. e. a, b c, d), its row (A, $\underline{\text{A}}$) marginal is multiplied by its column (B, $\underline{\text{B}}$) marginal, and that product is divided by the sample size (N).

		Conditioned B_{t}		
		TRUE	FALSE	
Condition	TRUE	a	b	A
A_{t}	FALSE	c	d	$\underline{\text{A}}$
		B	$\underline{\text{B}}$	N

Tabelle 10: Chi square and a 2x2 table

Definition 2.20 (**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.

$$\begin{aligned}pValue_{\text{lt}}\left(A_{\text{t}} \leftarrow B_{\text{t}}\right) &\equiv 1-e^{-(1-p(A_{\text{t}} \leftarrow B_{\text{t}}))} \\ &\equiv 1-e^{-(c/N)}\end{aligned} \tag{44}$$

A low p-value indicates statistical significance.

From another point of view, table 11 provides an example of the theoretical distribution of a necessary condition too.

Tabelle 11: Necessary condition.

		Conditioned B_{t}		
		YES	NO	
Condition A_{t}	YES	1	1	2
	NO	0	1	1
		1	2	3

Definition 2.21 (Fisher's exact one sided right tailed test of a necessary condition relationship).

Under some circumstances, a certain sampling distribution of a test statistic (like necessary condition relationship) is only approximately equal to the theoretical chi-squared distribution and a chi-squared goodness of fit test (Barukčić, 2019b, 2019c) might provide only approximate significance values. In point of fact, if **the expected values calculated** are too low or below 5, Fisher's Exact Test is an alternative to a chi-square test and it is more appropriate to consider the use Fisher's Exact test in place of chi-square test especially for 2×2 tables. Fisher's exact test is used especially when sample sizes are small, but the same is valid for all sample sizes. However, Fisher's exact test can be used even for tables that are larger than 2×2. Sir Ronald Aylmer Fisher (1890 – 1962) published an exact statistical significance test ("*Fisher's exact test*") (Fisher, 1922) for the analysis of contingency tables *valid for all sample sizes*.
The null hypothesis of Fisher's Exact test is that the rows and the columns of the 2 × 2 table are independent, such that the probability of a subject being in a particular row is not influenced by being in a particular column.
Table 12 may provide an overview of the foundation of Fisher's Exact test.

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

Tabelle 12: Two by two table and Fisher's exact test

Fisher's exact test is a conservative test which is based on the hyper geometric distribution and not on the calculation of probabilities from a distribution (as in t-tests or chi-square). The hyper geometric (HGD) probability mass function is given by

$$\begin{aligned} p_{\text{HGD}}\left(X=a\right) &\equiv \left(\frac{\binom{A}{a} \times \binom{N-A}{B-a}}{\binom{N}{B}} \right) \\ &\equiv \left(\frac{\binom{A}{a} \times \binom{A}{c}}{\binom{N}{B}} \right) \end{aligned} \tag{45}$$

Fisher's exact test can be used on more robust data sets too. Consider sampling a population of size N that has B objects with O and $\underline{B}$ with $\underline{O}$. Draw a sample of A objects and find a objects with O (see table 13).

		Sampling a population		
		O	$\underline{O}$	
In Sample	YES	a	b	A
(Not In Sample)	NO	c	d	$\underline{A}$
		B	$\underline{B}$	N

Tabelle 13: Two by two table and Fisher's exact test II

Then there are

$$\binom{N}{A} \tag{46}$$

possible samples. Of these,

$$\binom{B}{a} \tag{47}$$

is the number of ways of choosing O in a sample of size B, while

$$\binom{\underline{B}}{b} \tag{48}$$

is the number of ways of choosing not-O or $\underline{O}$ in a sample of size

$$N - B = \underline{B} \tag{49}$$

Because these are independent, there are

$$\binom{B}{a} \times \binom{\underline{B}}{b} \tag{50}$$

ways of choosing a Os and b not-Os.

Therefore, the probability of choosing a

$$\begin{aligned} Os &\equiv \frac{\binom{B}{a} \times \binom{\underline{B}}{b}}{\binom{N}{A}} \\ &\equiv \frac{\frac{B!}{a! \times c!} \times \frac{\underline{B}!}{b! \times d!}}{\frac{N!}{A! \times \underline{A}!}} \\ &\equiv \frac{B! \times \underline{B}! \times A! \times \underline{A}!}{N! \times a! \times b! \times c! \times d!} \end{aligned} \tag{51}$$

which is Fisher's exact test formula given usually. In order to calculate the significance of the observed data, i.e. the total probability of observing data as extreme or more extreme if the null hypothesis true, we have to calculate the P value of a one-tailed test.

The *one sided right tailed (rt) P Value* under conditions of the validity of the hyper-geometric (Gonin, 1936; Huygens & van Schooten, 1657; Pearson, 1899) distribution (HGD) is calculated according to the following formula (Barukčić, 2020; Scheid, 1992).

$$pValue(HGD)_{\text{rt}}\left(X \geq a\right) \equiv 1 - \sum_{t=0}^{a-1} \left(\frac{\binom{A}{t} \times \binom{N-A}{B-t}}{\binom{N}{B}} \right) \tag{52}$$

Definition 2.22 (**Sufficient condition [*Conditio per quam*]**).

Mathematically, the sufficient condition (IMP) relationship, denoted by $p(A_t \rightarrow B_t)$ in terms of probability theory, is defined as

$$\begin{aligned} p\left(A_t \rightarrow B_t\right) &\equiv p\left(a_t\right) + p\left(c_t\right) + p\left(d_t\right) \\ &\quad \frac{N \times \left(p\left(a_t\right) + p\left(c_t\right) + p\left(d_t\right)\right)}{N} \\ &\equiv \frac{a + c + d}{N} \\ &\equiv +1 \end{aligned} \tag{53}$$

Let us assume the relationship $p\left(A_t \rightarrow B_t\right)$ as proof, secured and given. Let $p\left(C_t\right)$ denote the probability of another event C_t. The conditio per quam relationship is one of the many foundations of mathematical techniques for an industrial mass-identifications of antidotes too. An event which can counteract the occurrence of another event can be understood something as an anti-dot event. Under conditions where $p\left(A_t \rightarrow B_t\right) + p\left(C_t\right) \equiv +1$, event C_t is an anti-dot of event A_t.

Definition 2.23 (**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 (Barukčić, 2018b, 2018c) with degree of freedom (d. f.) of d. f. = 1 is calculated as

$$\begin{aligned} \tilde{\chi}^2{}_{\text{Calculated}}\left(A_t \rightarrow B_t \mid A\right) &\equiv \frac{\left(a - \left(a + b\right)\right)^2}{A} + \\ &\quad \frac{\left(\left(c + d\right) - \underline{A}\right)^2}{\underline{A}} \\ &\equiv \frac{b^2}{A} + 0 \\ &\equiv \frac{b^2}{A} \end{aligned} \tag{54}$$

or equally as

$$\begin{aligned}\tilde{\chi}^2{}_{\text{Calculated}}\left(A_{\text{t}} \rightarrow B_{\text{t}} \mid \underline{B}\right) &\equiv \frac{\left(d-(b+d)\right)^2}{\underline{B}}+ \\ &\quad \frac{\left((a+c)-B\right)^2}{B} \\ &\equiv \frac{b^2}{\underline{B}}+0 \\ &\equiv \frac{b^2}{\underline{B}}\end{aligned} \tag{55}$$

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

Definition 2.24 (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.

$$\begin{aligned}pValue_{\text{lt}}\left(A_{\text{t}} \rightarrow B_{\text{t}}\right) &\equiv 1-e^{-(1-p(A_{\text{t}} \rightarrow B_{\text{t}}))} \\ &\equiv 1-e^{-(b/N)}\end{aligned} \tag{56}$$

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

Table 14 demonstrates the theoretical distribution of a sufficient condition.

Tabelle 14: Sufficient condition.

		Conditioned B_t		
		YES	NO	
Condition A_t	YES	1	0	1
	NO	1	1	2
		2	1	3

Definition 2.25 (Necessary and sufficient conditions [*EQV*]).

Mathematically, the necessary and sufficient condition (EQV) relationship, denoted by $p(A_t \leftrightarrow B_t)$ in terms of probability theory, is defined as

$$\begin{aligned}p\left(A_{\text{t}} \leftrightarrow B_{\text{t}}\right) &\equiv p\left(a_{\text{t}}\right)+p\left(d_{\text{t}}\right) \\ &\equiv \frac{N \times \left(p\left(a_{\text{t}}\right)+p\left(d_{\text{t}}\right)\right)}{N} \\ &\equiv \frac{a+d}{N} \\ &\equiv +1\end{aligned} \tag{57}$$

Definition 2.26 (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 (Barukčić, 2018b, 2018c) with degree of freedom (d. f.) of d. f. = 1 is calculated as

$$\begin{aligned}\tilde{\chi}^2{}_{\text{Calculated}}\left(A_{\text{t}} \leftrightarrow B_{\text{t}} \mid A\right) &\equiv \frac{\left(a-(a+b)\right)^2}{A}+ \\ &\quad \frac{d-\left((c+d)\right)^2}{\underline{A}} \\ &\equiv \frac{b^2}{A}+\frac{c^2}{\underline{A}}\end{aligned} \tag{58}$$

or equally as

$$\begin{aligned}\tilde{\chi}^2{}_{\text{Calculated}}\left(A_t \leftrightarrow B_t \mid B\right) &\equiv \frac{\left(a-(a+c)\right)^2}{B}+ \\ &\quad \frac{d-\left((b+d)\right)^2}{\underline{B}} \\ &\equiv \frac{c^2}{B}+\frac{b^2}{\underline{B}}\end{aligned} \tag{59}$$

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.

Definition 2.27 (The left-tailed p Value of a necessary and sufficient condition relationship).

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

$$\begin{aligned}pValue_{\text{lt}}\left(A_t \leftrightarrow B_t\right) &\equiv 1-e^{-(1-p(A_t \leftrightarrow B_t))} \\ &\equiv 1-e^{-((b+c)/N)}\end{aligned} \tag{60}$$

In this context, a low p-value indicates again a statistical significance. Table 15 may provide an overview of the theoretical distribution of a necessary and sufficient condition.

Tabelle 15: Necessary and sufficient condition.

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

For the purposes at hand, as should be immediately apparent, it is obviously clear, straightforward, deeply important and beyond any question that in analytic philosophy, accurate specifications of necessary and sufficient conditions (NSC) play already a central and vital role while logical fallacies cannot be excluded in general. In analytic philosophy, the concept of necessary and sufficient conditions is based on notions like an antecedent and a consequent too whilst analytic philosophy is not ensuring permanently that an antecedent and a consequent are given or treated at the same (period of) time t. Finally, some known and invalid inferential forms reasoning may follow (affirming the consequent, denying the antecedent et cetera). In contrast to analytic philosophy, the probability based concept of necessary and sufficient conditions is grounded on **events occurring at the same (period of) time t**. Another important clarification regarding necessary and sufficient conditions is the fact that NSC are equally converses of each other. In this case, there is a kind of strange mirroring as follows: $A_t \leftarrow B_t \equiv B_t \rightarrow A_t$. On this account, A_t being a sufficient condition of B_t is logically equivalent to B_t being a necessary condition of A_t (and vice versa). However, this has no influence on the definition of necessary and sufficient conditions. Necessary and sufficient conditions are defined as $(A_t \leftrightarrow B_t) \equiv (A_t \leftarrow B_t) \cap (A_t \rightarrow B_t)$ and not as $(A_t \leftrightarrow B_t) \equiv (A_t \leftarrow B_t) \cap (B_t \rightarrow A_t)$ where $\cap$ denote conjugation. The account of necessary and sufficient conditions just outlined is particularly different from the concept of logical conditions. It is, then, worth making the obvious point that a causal relationship may posses many different features and a very serious and fundamental question may arise: **can an effect$_t$ as such occur without a cause$_t$**? If we answer this question to the positive, we must accept equally that events can occur without a cause or that a causeless effect may exist or that a causeless change is possible in principle. In last consequence, such a scientific attitude ultimately demand us to abandon **the principle of causality** in general. In contrast to such an **anti causal position** it is clear that the principle of causality implies too that a cause$_t$ is needed for an effect$_t$ to occur. A cause$_t$ is a necessary condition of an effect$_t$. In other words, **without** a cause$_t$ **no** effect$_t$ or a cause and a necessary condition are identical. However, it is inappropriate to treat a necessary condition of an event (effect$_t$) as being at the same (period of) time t a sufficient condition

for the same event ($effect_t$) to occur. Such an attitude may end up at a causal fallacy. A necessary condition of an event is a condition which must be present for another event ($effect_t$) to occur. A necessary condition must be given in order for event ($effect_t$) to occur, but it alone does not provide sufficient cause for the occurrence of the event ($effect_t$). In contrast to a necessary condition, a sufficient condition is a condition that will produce the event ($effect_t$) to occur. Therefore and besides of **the identity of a cause and a necessary condition**, a cause as such cannot be reduced only to a necessary condition, a cause at the same (period of) time t is equally different from a necessary condition, both are logically not equivalent. **The difference between a cause and a necessary condition** determines the fact, that a cause is equally much more than only a necessary condition. In contrast to a necessary condition, an event, which is $cause_t$ should also ensure too that another event ($effect_t$) need to occur. To bring it to the point, a cause is at the same (period of) time t a sufficient condition of an effect too. In the light of these considerations, another determining part of a causal relationship is the relation **if** $cause_t$ **then** $effect_t$. But now let us notice what is strangest about the fundamental relationship between a cause and an effect. A $cause_t$ at a certain (period of) time t is both, a necessary and sufficient condition of an $effect_t$.

It seems difficult to bring forward an appropriate comment to all **anti causal authors** who wrote on the relation between cause and effect. J. L. Mackie's effectively anti causal position may serve as an example and as a representative for the numerous others. J. L. Mackie's theoretically very inappropriate approach to the notion cause and effect can be found in his paper 'Causes and Conditions'(see Mackie, 1965). Completely in line with David Hume's (1711 - 1776) meanwhile outdated account to the relation of a cause and an effect, Mackie writes: ". . . a cause is . . . an event which precedes the event of which it is the cause, and is both necessary and sufficient for the latter's occurrence"(see Mackie, 1965, p. 245) In other sense, we must accept that the logical fallacy that a cause is temporally prior in time to an effect. Based on his flawed approach to the nature of causation, Mackie is inventing enthusiastically a logical fallacy abbreviated as **INUS**, a very special, artificial, logically inconsistent and unrealistic approach to the relationship between a cause and an effect. "The so-called cause is . . . an insufficient but necessary part of a condition which is itself unnecessary but sufficient for the result [effect, author]. "(see Mackie, 1965, p. 245) More or less, Mackie himself reduces defectively a cause as such only to a sufficient condition. Mackie is trying to convince the reader that a cause is not a necessary condition too. Really not, a ". . . cause is . . . a condition which is . . . sufficient for the result [effect, author]. "(see Mackie, 1965, p. 245). However, this doesn't necessarily mean that both are really to be equated according to Mackie. Besides of all, Mackie is compelled to admit that a cause is at the end quite different from a sufficient condition too even if not a necessary condition. In contrast to a pure sufficient condition, a cause is only ". . . an insufficient but necessary part of a condition . . . "(see Mackie, 1965, p. 245), whatever this may mean. Whether it is possible or not to decompose a sufficient condition into single parts like a sufficient part and a non sufficient part or into a necessary part and a not necessary part like $A_t \equiv (sufficient\ part_t \cup not\ sufficient\ part_t) \cap (necessary\ part_t \cup not\ necessary\ part_t)$ is not an issue which appears to be able to affect the nature of a sufficient condition. A sufficient condition is a sufficient condition or it is not a sufficient condition independently of any single parts which may determine the same. Unfortunately, this not the point where Mackie's completely unrealistic and unnecessary narration ends. Mackie tries to convince us that a ". . . cause is . . . a condition which is itself unnecessary . . . for the result [effect, author]. "(see Mackie, 1965, p. 245) Mackie imposes its own flawed understanding of the relation between cause and effect on others so thoughtlessly, that even the toughest among the patient is hardly able to bear. According to Mackie, **a cause is not a necessary condition of an effect**. In other words, according to Mackie, **an effect can occur without a cause**! In last consequence, Mackie is giving up the principle of causality. Last but not least, Mackie's so-called INUS logical fallacy is an insufficient but necessary part of a failed, brutal theoretical attack on the principle of causality which is itself unnecessary but sufficient for non-sense produced by the author himself.

A final assessment of the issue necessary and sufficient conditions and causation and of the need for further action to be taken with regard to the recognition or the detection of causal relationships (from data) is the fundamental credo that a necessary and sufficient condition relationship is able to recognise or to detect causal relationships (from data). Table 16 provides an illustration of the theoretical distribution of a necessary and sufficient condition with respect to the causal relationship.

Tabelle 16: Causal relationship.

		Effect B_t		
		YES	NO	
Cause A_t	YES	1	0	1
	NO	0	1	1
		1	1	2

Many times, studies or experiments may be the next best method of addressing questions about the causal relationship between two factors like A_t and B_t. However, when performing real-word experiments or other investigations, bias of different kind (subjective and objective factors) including logical fallacies need to be considered in detail and the possibility to recognise the causal relationship between the two factors A_t and B_t while relying only on the **necessary and sufficient condition** relationship may be very rarely the case. Therefore and in general, it is necessary that the same study or different studies independently of each other provide significant evidence of a necessary condition relationship between the factors factors like A_t and B_t and equally of a sufficient condition relationship between the same factors A_t and B_t and of course, if possible, of a necessary and sufficient condition relationship between factors A_t and B_t. At least for these reasons and in order to avoid misconceptions about a causal relation between the factors A_t and B_t, we always require additional tools like the **causal relationship** k to be able to recognise a causal relationship between factors like A_t and B_t from data.

Definition 2.28 (**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 the principle of causality 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, 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 a logically inconsistent (Barukčić, 2011, 2014, 2016a), completely unnecessary and confusing uncertainty principle (Heisenberg, 1927) 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, 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 (Barukčić, 2011, 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, 1780). 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, 1780) 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, 1780) With more or less meaningless or none progress on the matter in hand even in the best possible conditions, it is not surprising that authors are suggesting more and more different approaches and models for causal inference. Indeed, the hope is justified that logically consistent *statistical methods of causal inference* can help scientist to achieve so much with so little. One of the

methods of causal inference in Bio-sciences are based on the known *Henle (Henle, 1840) (1809–1885) - Koch (Koch, 1878) (1843–1910) postulates* (Carter, 1985) which are applied especially for the identification of a causative agent of an (infectious) disease. However, the pathogenesis of most chronic diseases is more or less very complex and potentially involves the interaction of several factors. In practice, from the 'pure culture' requirement of the Henle-Koch postulates insurmountable difficulties may emerge. In light of subsequent developments (PCR methodology, immune antibodies et cetera) it is appropriate to review the full validity of the Henle-Koch postulates in our days. In 1965, Sir Austin Bradford Hill (Hill, 1965) published nine criteria (the '*Bradford Hill Criteria* ') in order to determine whether observed epidemiologic associations are causal. Somewhat worrying, is at least the fact that, Hill's "... fourth characteristic is *the temporal relationship of the association* " and so-to-speak just a reformulation of the '*post hoc ergo propter hoc'(Barukčić, 1989; Woods & Walton, 1977)* logical fallacy through the back-door and much more then this. It is questionable whether association as such can be treated as being identical with causation. Unfortunately, due to several reasons, it seems therefore rather problematic to rely on Bradford Hill Criteria carelessly. Meanwhile, several other and competing mathematical or statistical approaches for causal inference have been discussed (Barukčić, 1989, 1997, 2005, 2016b, 2017a, 2017b; Bohr, 1937; Dempster, 1990; Espejo, 2007; Hessen, 1928; Hesslow, 1976, 1981; Korch, 1965; Pearl, 2000; Schlick, 1931; Suppes, 1970; Zesar, 2013) or even established (Barukčić, 1989, 1997, 2005, 2016b, 2017a, 2017b). 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? Nonetheless, mathematically, the causal relationship (Barukčić, 1989, 1997, 2005, 2016b, 2017a, 2017b) between a cause A_t and an effect B_t, denoted by $k(A_t, B_t)$ in terms of probability theory, is defined *at each single (Thompson, 2006) Bernoulli trial t* as

$$\begin{aligned} k\left(A_t, B_t\right) \equiv & \frac{\sigma\left(A_t, B_t\right)}{\sigma\left(A_t\right) \times \sigma\left(B_t\right)} \\ \equiv & \frac{p\left(A_t \cap B_t\right) - p\left(A_t\right) \times p\left(B_t\right)}{\sqrt[2]{\left(p\left(A_t\right) \times \left(1 - p\left(A_t\right)\right)\right) \times \left(p\left(B_t\right) \times \left(1 - p\left(B_t\right)\right)\right)}} \end{aligned} \tag{61}$$

where σ (A_t , B_t) denotes the co-variance between a cause A_t and an effect B_t *at every single Bernoulli trial t*, σ (A_t) denotes the standard deviation of a cause A_t at the same single Bernoulli trial t, σ (B_t) denotes the standard deviation of an effect B_t at same single Bernoulli trial t. Table 17 provides an overview of the definition of the causal relationship k.

		Effect B_t		
		TRUE	FALSE	
Cause 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

Tabelle 17: the causal relationship k

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, 2017b) 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, 1904), 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.

Definition 2.29 (Fisher's exact test and the causal relationship k).

Under some circumstances, the significance of a causal relationship k can be tested by Fisher's exact statistical significance test ("*Fisher's exact test*") (Fisher, 1922) for the analysis of contingency tables too.
The null hypothesis of Fisher's Exact test is that a cause and an effect as illustrated by the 2×2 table 18 are independent.

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

Tabelle 18: Fisher's exact test and causation

The observed data are determined by several factors one of which is the study design too. In order to evaluate the significance of the observed data, i.e. the total probability of observing data as extreme or more extreme if the null hypothesis true, it is necessary to calculate a P value i. e. of a one-tailed test.
The *one sided right tailed (rt) P Value* under conditions of the validity of the hyper-geometric (Gonin, 1936; Huygens & van Schooten, 1657; Pearson, 1899) distribution (HGD) is calculated according to the following formula (Barukčić, 2020; Scheid, 1992).

$$pValue(HGD)_{\text{rt}}\left(X \geq a\right) \equiv 1 - \sum_{t=0}^{a-1} \left(\frac{\binom{A}{t} \times \binom{N-A}{B-t}}{\binom{N}{B}} \right) \tag{62}$$

The *one sided left tailed (lt) P Value* under conditions of the validity of the hyper-geometric (Gonin, 1936; Huygens & van Schooten, 1657; Pearson, 1899) distribution (HGD) is calculated according to the following formula.

$$pValue(HGD)_{\text{lt}}\left(X \leq a\right) \equiv \sum_{t=0}^{a} \left(\frac{\binom{A}{t} \times \binom{N-A}{B-t}}{\binom{N}{B}} \right) \tag{63}$$

C. Axioms

Axiom I. Lex identitatis

$$+1 = +1 \tag{64}$$

Axiom II. Lex contradictionis

$$+0 = +1 \tag{65}$$

Axiom III. Lex negationis

$$\neg \times 0 = 1 \tag{66}$$

where $\neg$ denotes (logical) negation.

III. Results

Theorem 3.1 (Helicobacter pyolori is neither a cause nor the case of pancreatic cancer)**.** *Helicobacter pylori infection has been found to increase risk for pancreatic cancer. Huang et al. (Huang et al., 2017) provided some data on this relationship.*

Null hypothesis 3.1. *A Helicobacter pylori infection **is** a necessary condition (conditio sine qua non) of pancreatic cancer. In other words, **without** a Helicobacter pylori infection **no** pancreatic cancer.*
A statistical significant difference between an observed (sample) distribution of the conditio sine qua non relationship and the expected distribution of the conditio sine qua non relationship is not given ($\alpha = .05$).

Alternative hypothesis 3.1. *A Helicobacter pylori infection **is not** a necessary condition (conditio sine qua non) of pancreatic cancer.*
A statistical significant difference between an observed (sample) distribution of the conditio sine qua non relationship and the expected distribution of the conditio sine qua non relationship is given ($\alpha = .05$).

Proof by induction (experiment/study). Huang et al. (Huang et al., 2017) provided data about the relationship between a Helicobacter pylori infection and pancreatic cancer. The data available and the statistical analysis of these data are illustrated in detail by table 19.

Tabelle 19: Helicobacter pylori and pancreatic cancer.

		Pancreatic cancer		
		YES	NO	
Helicobacter pylori	YES	196	206	402
	NO	252	242	494
		448	448	896

Causal relationship k =	-0,0224
p Value right tailed (HGD) =	0,7700
p (SINE) =	0,7188
$\tilde{\chi}^2$ (SINE | B_t) =	141,7500
$\tilde{\chi}^2$ (SINE | $\underline{A}_t$) =	128,5506
p Value right tailed (HGD) =	0,7700
p Value (SINE) =	0,2452
p (IMP) =	0,7701
$\tilde{\chi}^2$ (IMP | A_t) =	105,5622
$\tilde{\chi}^2$ (IMP | $\underline{B}_t$) =	94,7232
p Value right tailed (HGD) =	0,7700
p Value (IMP) =	0,2054
p (SINE∩IMP) =	0,4888
$\tilde{\chi}^2$ (SINE∩IMP)$_1$ =	234,1128
$\tilde{\chi}^2$ (SINE∩IMP)$_2$ =	236,4732
p Value right tailed (HGD) =	0,7700
p Value (SINE∩IMP) =	0,4002
p (EXCL) =	0,7813
$\tilde{\chi}^2$ (EXCL| A_t) =	95,5622
$\tilde{\chi}^2$ (EXCL| B_t) =	85,7500
p Value (EXCL) =	0,1965
p(IOI)=	0,0513
p(IOU)=	0,0513

The data of the study of Huang et al. (Huang et al., 2017) are of very good quality. The index of unfairness (see Barukčić, 2019c) of the study of Huang et al. (Huang et al., 2017), abbreviated as p(IOU), is $p(IOU) \equiv 0,0513$ and is less than 0,30. To some extent the data published are not completely biased and can be analysed for necessary

conditions, for sufficient conditions or for necessary and sufficient conditions. The index of independence (see Barukčić, 2019b) of the study of Huang et al. (Huang et al., 2017), abbreviated as p(IOI), has been calculated as $p(IOI) \equiv 0,0513$ and is less than 0,30. The data published are not completely biased and can be analysed for an exclusion relationship or for causal relationships k. The causal relationship k has been calculated as $k = -0,0224\,(p\ Value\ (HGD)_{\text{right tailed}}\,(X \geq 196) \equiv 0,7700)$ and is statistically not significant. The data of the study yield a negative causal relationship between a Helicobacter pylori infection and pancreatic cancer $(p\ Value\ \equiv 0,7700)$. The data have been analysed to prof the null-hypothesis **without** a Helicobacter pylori infection **no** pancreatic cancer (conditio sine qua non) relationship. The $\tilde{\chi}^2$ goodness of fit test of a necessary condition relationship is found to be $\tilde{\chi}^2{}_{\text{Calculated}}\,(A_{\text{t}} \leftarrow B_{\text{t}} \mid B) \equiv \frac{c^2}{B} \equiv \frac{252^2}{448} \equiv 141,7500$ which is significant because it is more than the α = 0.05 critical value for the chi-square distribution (3.841). The $\tilde{\chi}^2$ goodness of fit test of a necessary condition relationship was calculated in the same respect as $\tilde{\chi}^2{}_{\text{Calculated}}\,(A_{\text{t}} \leftarrow B_{\text{t}} \mid \underline{A}) \equiv \frac{c^2}{\underline{A}} \equiv \frac{252^2}{494} \equiv 128,5506$ which is significant too because it is again more than the α = 0.05 critical value for the chi-square distribution (3.841). There is a significant difference between the theoretical distribution of a necessary condition and the observed distribution of a necessary condition. The causal relationship has been found to be $k < 0$ (see Barukčić, 2018d, 2019b, 2019c). Thus far, the data analysed do not support the null-hypothesis: **without** a Helicobacter pylori infection **no** pancreatic cancer. The left-tailed (lt) p Value (Barukčić, 2019d) of the conditio sine qua non relationship has been documented as $pValue_{\text{lt}}\,(A_{\text{t}} \leftarrow B_{\text{t}}) \equiv 1 - e^{-(1-p(A_{\text{t}} \leftarrow B_{\text{t}}))} \equiv 1 - e^{-(c/N)} \equiv 1 - e^{-(252/896)} \equiv 0,2452$. In other words, the null-hypothesis $p\,(A_{\text{t}} \leftarrow B_{\text{t}}) \equiv +1$ cannot be accepted and need to be rejected $(pValue \equiv 0,2452)$. Based on the data of the study of Huang et al. (Huang et al., 2017), a pancreatic cancer can develop independently of a Helicobacter pylori infection. A Helicobacter pylori infection is not a necessary condition for pancreatic cancer to develop $(p\ Value \equiv 0,2452)$. Therefore, it does not make any sense to proof the data further for a causal relationship between a Helicobacter pylori infection and pancreatic cancer. According to the data of Huang et al. (Huang et al., 2017), a Helicobacter pylori infection is neither a cause nor the cause of pancreatic cancer.

□

Theorem 3.2 (Smoking is neither a cause nor the cause of pancreatic cancer)**.** *The relationship between cigarette smoking and pancreatic cancer risk has been discussed by many studies. The PanC4 study of Boseti at al. (Bosetti et al., 2012) provided high quality data with regard to this relationship.*

Null hypothesis 3.2. *Smoking of cigarettes is a necessary condition (conditio sine qua non) of pancreatic cancer. In other words,* ***without*** *smoking of cigarettes* ***no*** *pancreatic cancer.*
A statistical significant difference between an observed (sample) distribution of the conditio sine qua non relationship and the expected distribution of the conditio sine qua non relationship is not given ($\alpha = .05$).

Alternative hypothesis 3.2. *Smoking of cigarettes* ***is not*** *a necessary condition (conditio sine qua non) of pancreatic cancer.*
A statistical significant difference between an observed (sample) distribution of the conditio sine qua non relationship and the expected distribution of the conditio sine qua non relationship is given ($\alpha = .05$).

Proof by induction (experiment/study). Bosetti et al. (Bosetti et al., 2012) provided data about the relationship between smoking of cigarettes and pancreatic cancer. The data published by this study and the statistical analysis of these data are illustrated in detail by table 20.

Tabelle 20: Smoking and Pancreatic cancer .

		Pancreatic cancer		
		YES	NO	
Smoking	YES	4134	7333	11467
	NO	2373	5557	7930
		6507	12890	19397

Causal relationship k =	0,0638
p Value right tailed (HGD) =	0,0000
p (SINE) =	0,8777
$\tilde{\chi}^2$ (SINE | B_t) =	865,3956
$\tilde{\chi}^2$ (SINE | $\underline{A}_t$) =	710,1045
p Value right tailed (HGD) =	0,0000
p Value (SINE) =	0,1152
p (IMP) =	0,6220
$\tilde{\chi}^2$ (IMP | A_t) =	4.689,3598
$\tilde{\chi}^2$ (IMP | $\underline{B}_t$) =	4.171,6749
p Value right tailed (HGD) =	0,0000
p Value (IMP) =	0,3148
p (SINE∩IMP) =	0,4996
$\tilde{\chi}^2$ (SINE∩IMP)$_1$ =	5.399,4644
$\tilde{\chi}^2$ (SINE∩IMP)$_2$ =	5.037,0704
p Value right tailed (HGD) =	0,0000
p Value (SINE∩IMP) =	0,3937
p (EXCL) =	0,7869
$\tilde{\chi}^2$ (EXCL| A_t) =	1.490,3598
$\tilde{\chi}^2$ (EXCL| B_t) =	2.626,3956
p Value (EXCL) =	0,1919
p(IOI)=	0,2557
p(IOU)=	0,0734

The index of unfairness (see Barukčić, 2019c) of the study of Bosetti et al. (Bosetti et al., 2012), abbreviated as p(IOU), is $p(IOU) \equiv 0,0734$ and is less than 0,30. To some extent the data published by Bosetti et al. (Bosetti et al., 2012) are not completely biased and can be analysed for necessary conditions, for sufficient conditions or for necessary and sufficient conditions. The index of independence (see Barukčić, 2019b) of the study of Bosetti et al. (Bosetti et al., 2012), abbreviated as p(IOI), has been calculated as $p(IOI) \equiv 0,2557$ and is

not less than 0,30. The data published are not completely free of bias and cannot be analysed for an exclusion relationship or for causal relationships k without any restriction. The causal relationship k has been calculated as $k = +0,0638\,(p\ Value\ (HGD)_{\text{right tailed}}\,(X \geq 4134) \equiv 0,0000)$ and is statistically significant. The data of the study provide evidence of a positive causal relationship between smoking of cigarettes and pancreatic cancer $(p\ Value\ \equiv 0.0000)$. The data have been analysed in order to prof the null-hypothesis **without** smokoing of cigarettes **no** pancreatic cancer (conditio sine qua non) relationship. The $\tilde{\chi}^2$ goodness of fit test of a necessary condition relationship is found to be $\tilde{\chi}^2{}_{\text{Calculated}}\,(A_{\text{t}} \leftarrow B_{\text{t}} \mid B) \equiv \frac{c^2}{B} \equiv \frac{2373^2}{6507} \equiv 865,3956$ which is significant because it is more than the α = 0.05 critical value for the chi-square distribution (3.841). The $\tilde{\chi}^2$ goodness of fit test of a necessary condition relationship was calculated in the same respect as $\tilde{\chi}^2{}_{\text{Calculated}}\,(A_{\text{t}} \leftarrow B_{\text{t}} \mid \underline{A}) \equiv \frac{c^2}{\underline{A}} \equiv \frac{2373^2}{7930} \equiv 710,1045$ which is significant too because it is again greater than the α = 0.05 critical value for the chi-square distribution (3.841). There is a significant difference between the theoretical distribution of a necessary condition and the observed distribution of a necessary condition. The causal relationship has been found to be $k > 0$ (see Barukčić, 2018d, 2019b, 2019c). Thus far, the data analysed are not self contradictory and do not support the null-hypothesis: **without** smoking of cigarettes **no** pancreatic cancer. The left-tailed (lt) p Value (Barukčić, 2019d) of the conditio sine qua non relationship has been documented as $p\ Value_{\text{lt}}\,(A_{\text{t}} \leftarrow B_{\text{t}}) \equiv 1 - e^{-(1-p(A_{\text{t}} \leftarrow B_{\text{t}}))} \equiv 1 - e^{-(c/N)} \equiv 1 - e^{-(2373/19397)} \equiv 0,1152$. In other words, the null-hypothesis $p\,(A_{\text{t}} \leftarrow B_{\text{t}}) \equiv +1$ cannot be accepted $(pValue \equiv 0,1152)$. Based on the data of the study of Bosetti et al. (see Bosetti et al., 2012), the conclusion is justified that the null-hypothesis: **without** smoking of cigarettes **no** pancreatic cancer $(p\ Value \equiv 0,1152)$ need to be rejected. In other words, **it is possible to suffer from pancreatic cancer without consumption of cigarettes at all**. To establish a cause effect relationship, it is necessary to provide evidence of a necessary condition too. The data of Bosetti et al. (see Bosetti et al., 2012) failed to provide any evidence that smoking of cigarettes is a necessary condition of pancreatic cancer. Therefore, a further analysis of the data of Bosetti et al. (see Bosetti et al., 2012) for causal relationship is without any sense.

□

Theorem 3.3 (Diabetes mellitus is neither a cause nor the cause of pancreatic cancer)**.** *Epidemiological and other investigations have found that type 2 diabetes mellitus is more or less the third modifiable risk factor for pancreatic cancer after cigarette smoking and obesity (see D. Li, 2012). The study design of many studies, which provided data on this topic, was not very convincing (i. e. p(IOU) to high). Therefore, the relationship between diabetes mellitus and pancreatic cancer is examined in this publication by way of an example in detail below with reference to the data provided by Bosetti et al. (see Bosetti et al., 2014) .*

Null hypothesis 3.3. *Diabetes mellitus **is** a necessary condition (conditio sine qua non) of pancreatic cancer. In other words, **without** diabetes mellitus **no** pancreatic cancer.*
A statistical significant difference between an observed (sample) distribution of the conditio sine qua non relationship and the expected distribution of the conditio sine qua non relationship is not given ($\alpha = .05$).

Alternative hypothesis 3.3. *Diabetes mellitus **is not** a necessary condition (conditio sine qua non) of pancreatic cancer. In other words, it is possible to suffer from pancreatic cancer **without** suffering from diabetes mellitus.*
A statistical significant difference between an observed (sample) distribution of the conditio sine qua non relationship and the expected distribution of the conditio sine qua non relationship is given ($\alpha = .05$).

Proof by induction (experiment/study). Bosetti et al. (see Bosetti et al., 2014) provided data about the relationship between diabetes mellitus and pancreatic cancer. The data available publicly and the statistical analysis of these data are illustrated in detail by table 21.

Tabelle 21: Diabetes mellitus and pancreatic cancer.

		Pancreatic cancer		
		YES	NO	
Diabetes mellitus	YES	1767	1284	3051
	NO	6404	12629	19033
		8171	13913	22084

Causal relationship k =	+0,1734
p Value right tailed (HGD) =	0,0000
p (SINE) =	0,7100
$\tilde{\chi}^2$ (SINE | B_t) =	5.019,1183
$\tilde{\chi}^2$ (SINE | $\underline{A_t}$) =	2.154,7426
p Value right tailed (HGD) =	0,0000
p Value (SINE) =	0,2517
p (IMP) =	0,9419
$\tilde{\chi}^2$ (IMP | A_t) =	540,3658
$\tilde{\chi}^2$ (IMP | $\underline{B_t}$) =	118,4975
p Value right tailed (HGD) =	0,0000
p Value (IMP) =	0,0565
p (SINE∩IMP) =	0,6519
$\tilde{\chi}^2$ (SINE∩IMP)$_1$ =	2.695,1084
$\tilde{\chi}^2$ (SINE∩IMP)$_2$ =	5.137,6159
p Value right tailed (HGD) =	0,0000
p Value (SINE∩IMP) =	0,2940
p (EXCL) =	0,9200
$\tilde{\chi}^2$ (EXCL| A_t) =	1.023,3658
$\tilde{\chi}^2$ (EXCL| B_t) =	382,1183
p Value (EXCL) =	0,0769
p(IOI)=	0,2318
p(IOU)=	0,4918

The index of unfairness (see Barukčić, 2019c) of the study of Bosetti et al. (see Bosetti et al., 2014), abbreviated as p(IOU), is $p(IOU) \equiv 0,4918$ and is greater than 0,30. The data published by Bosetti et al. (see Bosetti et al., 2014) are potentially biased and can be re-analysed for necessary conditions, for sufficient conditions

or for necessary and sufficient conditions only with some restrictions. However, the index of independence (see Barukčić, 2019b) of the study of Bosetti et al. (see Bosetti et al., 2014), abbreviated as p(IOI), is calculated as $p(IOI) \equiv 0,2318$ and is less than 0,30. The data published by Bosetti et al. (see Bosetti et al., 2014) are not absolutely biased can be re-analysed for an exclusion relationship or for causal relationships k and to some extent even for necessary conditions, for sufficient conditions or for necessary and sufficient conditions. The causal relationship k has been calculated as $k = +0,1734\,(p\ Value\ (HGD)_{\text{right tailed}}\,(X \geq 1767) \equiv 0,0000)$ and is statistically significant. Formally, the data of Bosetti et al. (see Bosetti et al., 2014) provide evidence of statistically significant positive causal relationship between diabetes mellitus and pancreatic cancer $(p\ Value\ \equiv 0,000)$.

However, this result is not enough to establish a causal relationship between diabetes mellitus and pancreatic cancer. The data should provide additional evidence of a conditio sine qua non relationship between diabetes mellitus and pancreatic cancer, of a conditio per quam relationship between diabetes mellitus and pancreatic cancer and if possible of a necessary and sufficient condition between diabetes mellitus and pancreatic cancer too. In the following, the data of Bosetti et al. (see Bosetti et al., 2014) analysed to prof the null-hypothesis **without** diabetes mellitus **no** pancreatic cancer (conditio sine qua non) relationship. The $\tilde{\chi}^2$ goodness of fit test of a necessary condition relationship between diabetes mellitus and pancreatic cancer is found to be ${\tilde{\chi}^2}_{\text{Calculated}}\,(A_{\text{t}} \leftarrow B_{\text{t}} \mid B) \equiv \frac{c^2}{B} \equiv \frac{6404^2}{8171} \equiv 5019,1183$ which is significant because it is greater than the α = 0.05 critical value for the chi-square distribution (3.841). The $\tilde{\chi}^2$ goodness of fit test of a necessary condition relationship between diabetes mellitus and pancreatic cancer is calculated in the same respect as ${\tilde{\chi}^2}_{\text{Calculated}}\,(A_{\text{t}} \leftarrow B_{\text{t}} \mid \underline{A}) \equiv \frac{c^2}{\underline{A}} \equiv \frac{6404^2}{19033} \equiv 2154,7426$ which is significant too because it is again greater than the α = 0.05 critical value for the chi-square distribution (3.841). There is a statistically significant difference between the theoretical distribution of a necessary condition and the observed distribution of a necessary condition. The causal relationship has been found to be $k > 0$ (see Barukčić, 2018d, 2019b, 2019c). Thus far, the data of Bosetti et al. (see Bosetti et al., 2014) are not self contradictory and do not support the null-hypothesis: **without** diabetes mellitus **no** pancreatic cancer. The left-tailed (lt) p Value (Barukčić, 2019d) of the conditio sine qua non relationship has been documented as $pValue_{\text{lt}}\,(A_{\text{t}} \leftarrow B_{\text{t}}) \equiv 1 - e^{-(1-p(A_{\text{t}} \leftarrow B_{\text{t}}))} \equiv 1 - e^{-(c/N)} \equiv 1 - e^{-(6404/22084)} \equiv 0,2517$ In other words, the null-hypothesis $p\,(A_{\text{t}} \leftarrow B_{\text{t}}) \equiv +1$ cannot be accepted $(pValue \equiv 0,2517)$. Based on the data of Bosetti et al. (see Bosetti et al., 2014), the conclusion is justified that the null-hypothesis **without** diabetes mellitus **no** pancreatic cancer $(p\ Value \equiv 0,2517)$ need to be rejected. However such a conclusion is compatible with real-life and human experience too, since many persons suffer from pancreatic cancer while at the same time not suffering from diabetes mellitus. In other words, diabetes mellitus is not necessary in order for pancreatic cancer to develop. A further comment on the statistical analysis of the data of Bosetti et al. (see Bosetti et al., 2014) as presented by table 21 is without any sense in this context.

□

Theorem 3.4 (Chronic pancreatitis is potentially a cause of pancreatic cancer)**.** *Pancreatic cancer is a highly aggressive malignancy with a median survival time of less than 1 year (B.-R. Li et al., 2014). Various studies concur that chronic pancreatitis is strongly associated with pancreatic cancer. However, the association claimed appears to diminish with long-term follow-up (Kirkegård et al., 2017).*

Null hypothesis 3.4. *Chronic pancreatitis is a sufficient condition (conditio per quam) of pancreatic cancer. In other words,* ***if*** *chronic pancreatitis* ***then*** *pancreatic cancer.*
A statistical significant difference between an observed (sample) distribution of the conditio per quam relationship and the expected distribution of the conditio per quam relationship is given ($\alpha = .05$).

Alternative hypothesis 3.4. *Chronic pancreatitis* ***is not*** *a sufficient condition (conditio per quam) of pancreatic cancer. In other words, the relationship* ***if*** *chronic pancreatitis* ***then*** *pancreatic cancer is not given.*
A statistical significant difference between an observed (sample) distribution of the conditio per quam relationship and the expected distribution of the conditio per quam relationship is given ($\alpha = .05$).

Proof by induction (experiment/study). Bo et al. (see Bo et al., 2019) conducted a hospital-based case-control study with 1,392 pancreatic cancer patients and 3,429 controls. The data of the study of Bo et al. (see Bo et al., 2019) and the statistical analysis of these data are illustrated in detail by table 22.

Tabelle 22: Chronic pancreatitis and pancreatic cancer.

		Pancreatic cancer		
		YES	NO	
Chronic pancreatitis	YES	38	14	52
	NO	1354	3415	4769
		1392	3429	4821

Causal relationship k =	+0,1019
p Value right tailed (HGD) =	0,0000
p (SINE) =	0,7191
$\tilde{\chi}^2$ (SINE | B_t) =	1.317,0374
$\tilde{\chi}^2$ (SINE | $\underline{A}_t$) =	384,4236
p Value right tailed (HGD) =	0,0000
p Value (SINE) =	0,2449
p (IMP) =	0,9971
$\tilde{\chi}^2$ (IMP | A_t) =	3,7692
$\tilde{\chi}^2$ (IMP | $\underline{B}_t$) =	0,0572
p Value right tailed (HGD) =	0,0000
p Value (IMP) =	0,0029
p (SINE∩IMP) =	0,7162
$\tilde{\chi}^2$ (SINE∩IMP)$_1$ =	388,1928
$\tilde{\chi}^2$ (SINE∩IMP)$_2$ =	1.317,0945
p Value right tailed (HGD) =	0,0000
p Value (SINE∩IMP) =	0,2471
p (EXCL) =	0,9921
$\tilde{\chi}^2$ (EXCL| A_t) =	27,7692
$\tilde{\chi}^2$ (EXCL| B_t) =	1,0374
p Value (EXCL) =	0,0079
p(IOI)=	0,2780
p(IOU)=	0,7005

The index of unfairness (see Barukčić, 2019c) of the study of Bo et al. (see Bo et al., 2019), abbreviated as p(IOU), is $p(IOU) \equiv 0,7005$ and is greater than 0,30. In light of these circumstances, there is a danger that the data published by Bo et al. (see Bo et al., 2019) are biased and of none or of very limited value for being analysed for necessary conditions, for sufficient conditions or for necessary and sufficient conditions. However, it needs to

be made clear that the index of independence (see Barukčić, 2019b) of the study of Bo et al. (see Bo et al., 2019), abbreviated as p(IOI), has been calculated as $p(IOI) \equiv 0,2780$ and is less than 0,30. This result indicates that the data published by Bo et al. (see Bo et al., 2019) are not absolutely biased and are to some extent of use for being analysed for an exclusion relationship or for causal relationships k and even for necessary conditions, for sufficient conditions or for necessary and sufficient conditions too. The causal relationship k has been calculated as $k = +0,1019\,(p\ Value\ (HGD)_{\text{right tailed}}\,(X \geq 38) \equiv 0.0000)$ and is statistically significant. The data of Bo et al. (see Bo et al., 2019) provide some statistical evidence of a significant positive causal relationship between chronic pancreatitis and pancreatic cancer $(p\ Value\ \equiv 0.0000)$.

Again, such a result alone is not very convincing to establish a cause effect relationship between chronic pancreatitis an pancreatic cancer. The data of Bo et al. (see Bo et al., 2019) have been analysed to prof the null-hypothesis **if** chronic pancreatitis **then** pancreatic cancer (conditio per quam) relationship. The $\tilde{\chi}^2$ goodness of fit test of a sufficient condition (conditio per quam) relationship is found to be $\tilde{\chi}^2{}_{\text{Calculated}}\,(A_{\text{t}} \rightarrow B_{\text{t}} \mid A) \equiv \frac{b^2}{A} \equiv \frac{14^2}{52} \equiv 3,7692$ which is not significant because it is less than the α = 0.05 critical value for the chi-square distribution (3.841). The $\tilde{\chi}^2$ goodness of fit test of a sufficient condition (conditio per quam) relationship was calculated in the same respect as $\tilde{\chi}^2{}_{\text{Calculated}}\,(A_{\text{t}} \rightarrow B_{\text{t}} \mid \underline{B}) \equiv \frac{b^2}{\underline{B}} \equiv \frac{14^2}{3429} \equiv 0,0572$ which is not significant either because it is again less than the α = 0.05 critical value for the chi-square distribution (3.841). In point of fact, there is no significant difference between the theoretical distribution of a sufficient condition and the observed distribution of a sufficient condition. The causal relationship has been found to be $k > 0$ (see Barukčić, 2018d, 2019b, 2019c), with the consequence that the data analysed are not self contradictory and do support the null-hypothesis: **if** chronic pancreatitis **then** pancreatic cancer. The left-tailed (lt) p Value (Barukčić, 2019d) of the sufficient condition (conditio per quam) relationship has been calculated as $pValue_{\text{lt}}\,(A_{\text{t}} \rightarrow B_{\text{t}}) \equiv 1 - e^{-(1-p(A_{\text{t}} \rightarrow B_{\text{t}}))} \equiv 1 - e^{-(b/N)} \equiv 1 - e^{-(14/4821)} \equiv 0,0029$. In other words, the null-hypothesis $p\,(A_{\text{t}} \rightarrow B_{\text{t}}) \equiv +1$ cannot be rejected $(pValue \equiv 0,0029)$.

□

Theorem 3.5 (Hyperlipidemia excludes pancreatic cancer and vice versa)**.** *Many studies explored the relationship between hyperlipidemia and the risk of pancreatic cancer, but the results of these studies are conflicting (J. Wang et al., 2015).*

Null hypothesis 3.5. *Hyperlipidemia excludes pancreatic cancer and vice versa. In other words, the occurrence/existence of Hyperlipidemia* ***excludes*** *the occurrence/existence of pancreatic cancer at the same (period of) time and vice versa.*
A statistical significant difference between an observed (sample) distribution of an exclusion relationship and the expected distribution of an exclusion relationship is not given ($\alpha = .05$).

Alternative hypothesis 3.5. *Hyperlipidemia* ***does not*** *exclude pancreatic cancer and vice versa.*
A statistical significant difference between an observed (sample) distribution of an exclusion relationship and the expected distribution of an exclusion relationship is given ($\alpha = .05$).

Proof by induction (experiment/study). Bo et al. (see Bo et al., 2019) provided data about the relationship between hyperlipidemia and pancreatic cancer. The data of Bo et al. (see Bo et al., 2019) and the statistical analysis these data are illustrated in detail by table 23.

Tabelle 23: Hyperlipidemia and pancreatic cancer.

		Pancreatic cancer		
		YES	NO	
Hyperlipidemia	YES	23	671	694
	NO	1369	2758	4127
		1392	3429	4821

Causal relationship k =	-0,2313
p Value left tailed (HGD) =	0,0000
p (SINE) =	0,7160
$\tilde{\chi}^2$ (SINE | B_t) =	1.346,3800
$\tilde{\chi}^2$ (SINE | $\underline{A}_t$) =	454,1219
p Value right tailed (HGD) =	1,0000
p Value (SINE) =	0,2472
p (IMP) =	0,8608
$\tilde{\chi}^2$ (IMP | A_t) =	648,7622
$\tilde{\chi}^2$ (IMP | $\underline{B}_t$) =	131,3039
p Value right tailed (HGD) =	1,0000
p Value (IMP) =	0,1299
p (SINE∩IMP) =	0,5769
$\tilde{\chi}^2$ (SINE∩IMP)$_1$ =	1.102,8841
$\tilde{\chi}^2$ (SINE∩IMP)$_2$ =	1.477,6839
p Value right tailed (HGD) =	1,0000
p Value (SINE∩IMP) =	0,3450
p (EXCL) =	0,9952
$\tilde{\chi}^2$ (EXCL| A_t) =	0,7622
$\tilde{\chi}^2$ (EXCL| B_t) =	0,3800
p Value (EXCL) =	0,0048
p(IOI)=	0,1448
p(IOU)=	0,5673

The index of unfairness (see Barukčić, 2019c) of the study of Bo et al. (see Bo et al., 2019), abbreviated as p(IOU), is $p(IOU) \equiv 0,5673$ and is greater than 0.3. To some extent the data published are potentially biased and can be analysed for necessary conditions, for sufficient conditions or for necessary and sufficient conditions only with great care. In contrast to the possible problems as indicated by the high p(IOU), the index of independence (see Barukčić, 2019b) of the study of Bo et al. (see Bo et al., 2019), abbreviated as p(IOI), has been calculated as

$p(IOI) \equiv 0,1448$ and is less than 0.25. The data published are not completely biased and are of use for the analysis of different measures of relationship like an exclusion relationship or for causal relationships k and even a necessary condition, a sufficient condition or a necessary and sufficient condition to some extent. The causal relationship k has been calculated as $k = -0,2313$ $(p\ Value\ (HGD)_{\text{right tailed}}\ (X \geq 23) \equiv 0.0000)$ and is statistically significant. The data of the study provide evidence of a negative causal relationship between hyperlipidemia and pancreatic cancer $(p\ Value\ \equiv 0.0000)$. In other words, hyperlipidemia excludes pancreatic cancer and vice versa.

Theoretically, it is indeed possible that an occurrence of hyperlipidemia may exclude the occurrence of pancreatic cancer and vice versa. The data of Bo et al. (see Bo et al., 2019) have been re-analysed to proof this null-hypothesis too. The $\tilde{\chi}^2$ goodness of fit test of an exclusion relationship has been calculated as $\tilde{\chi}^2{}_{\text{Calculated}}\left((A_{\text{t}} \mid B_{\text{t}}) \mid A\right) \equiv \frac{a^2}{A} \equiv \frac{23^2}{694} \equiv 0,7622$ which is not significant, because it is less than the α = 0.05 critical value for the chi-square distribution (3.841). In the same context, the $\tilde{\chi}^2$ goodness of fit test was calculated equally as $\tilde{\chi}^2{}_{\text{Calculated}}\left((A_{\text{t}} \mid B_{\text{t}}) \mid B\right) \equiv \frac{a^2}{B} \equiv \frac{23^2}{1392} \equiv 0,3800$ which is again not significant too because it is less than the α = 0.05 critical value for the chi-square distribution (3.841). The causal relationship has been found to be $k < 0$, with the consequence that there is no evidence that the data of Bo et al. (see Bo et al., 2019) are self contradictory (see Barukčić, 2018d, 2019b, 2019c) in this context. In other words, there is no significant statistical difference between the theoretical distribution of an exclusion relationship and the observed distribution of an exclusion relationship. The data analysed do support the null-hypothesis: hyperlipidemia excludes pancreatic cancer and vice versa. The left-tailed (lt) p Value (Barukčić, 2019d) of an exclusion relationship has been calculated as $pValue_{\text{lt}}\left(A_{\text{t}} \mid B_{\text{t}}\right) \equiv 1 - e^{-(1-p(A_{\text{t}}|B_{\text{t}}))} \equiv 1 - e^{-(a/N)} \equiv 1 - e^{-(23/4821)} \equiv 0,0048$ and is significant. In other words, the null hypothesis hyperlipidemia excludes pancreatic cancer and vice versa cannot be rejected $(p\ Value \equiv 0,0048)$.

□

Theorem 3.6 (Without being married no pancreatic cancer I)**.** *Wynder et al. (see Wynder et al., 1986) investigated the relationship between decaffeinated coffee consumption and pancreatic cancer and examined additional factors like cigarette smoking, marital status (single, married, divorced or separated, widowed), education, occupation, religion, alcohol drinking et cetera. These data are re-analysed.*

Null hypothesis 3.6. *Being married **is** a necessary condition (conditio sine qua non) of pancreatic cancer. In other words, **without** being married **no** pancreatic cancer.*
A statistical significant difference between an observed (sample) distribution of the conditio sine qua non relationship and the expected distribution of the conditio sine qua non relationship is not given ($\alpha = .05$).

Alternative hypothesis 3.6. *Being married **is not** a necessary condition (conditio sine qua non) of pancreatic cancer.*
A statistical significant difference between an observed (sample) distribution of the conditio sine qua non relationship and the expected distribution of the conditio sine qua non relationship is given ($\alpha = .05$).

Proof by induction (experiment/study). Wynder et al. (see Wynder et al., 1986) provided data about the relationship between marital status (single, married, divorced or separated, widowed) and pancreatic cancer. The data available and the statistical analysis of these data are illustrated in detail by table 24.

Tabelle 24: Marital status and pancreatic cancer.

		Pancreatic cancer		
		YES	NO	
Married	YES	227	646	873
	NO	11	49	60
		238	695	933

Causal relationship k =	0,0432
p Value right tailed (HGD) =	0,1200
p (SINE) =	0,9882
$\tilde{\chi}^2$ (SINE | B_t) =	0,5084
$\tilde{\chi}^2$ (SINE | $\underline{A_t}$) =	2,0167
p Value right tailed (HGD) =	0,1200
p Value (SINE) =	0,0117
p (IMP) =	0,3076
$\tilde{\chi}^2$ (IMP | A_t) =	478,0252
$\tilde{\chi}^2$ (IMP | $\underline{B_t}$) =	600,4547
p Value right tailed (HGD) =	0,1200
p Value (IMP) =	0,4996
p (SINE∩IMP) =	0,2958
$\tilde{\chi}^2$ (SINE∩IMP)$_1$ =	480,0419
$\tilde{\chi}^2$ (SINE∩IMP)$_2$ =	600,9631
p Value right tailed (HGD) =	0,1200
p Value (SINE∩IMP) =	0,5055
p (EXCL) =	0,7567
$\tilde{\chi}^2$ (EXCL| A_t) =	59,0252
$\tilde{\chi}^2$ (EXCL| B_t) =	216,5084
p Value (EXCL) =	0,2160
p(IOI)=	0,6806
p(IOU)=	0,1908

The index of unfairness (see Barukčić, 2019c) of the study of Wynder et al. (see Wynder et al., 1986), abbreviated as p(IOU), is $p(IOU) \equiv 0,1908$ and is less than 0.3. The data of Wynder et al. (see Wynder et al., 1986) are not completely biased and can be used for an analysis of necessary conditions, of sufficient conditions and of necessary and sufficient conditions. The index of independence (see Barukčić, 2019b) of the

study of Wynder et al. (see Wynder et al., 1986), abbreviated as p(IOI), has been calculated as $p(IOI) \equiv 0,6806$ and is greater than 0.3. The data published are potentially biased. An analysis of an exclusion relationship or of causal relationships k is possible only with great care. The causal relationship k has been calculated as $k = +0,0432\,(p\ Value\ (HGD)_{\text{right tailed}}\,(X \geq 227) \equiv 0,1200)$ and is statistically not significant. The data of the study of Wynder et al. (see Wynder et al., 1986) do not provide evidence of a significant positive causal relationship between marital status (single, married, divorced or separated, widowed) and pancreatic cancer $(p\ Value\ \equiv 0,1200)$.

However, even if the data of Wynder et al. (see Wynder et al., 1986) do not provide evidence of a significant cause-effect relationship between marital status (single, married, divorced or separated, widowed) and pancreatic cancer this does not exclude that marital status (single, married, divorced or separated, widowed) could be a necessary condition of pancreatic cancer. A cause is a necessary condition to but not vice versa. A necessary condition need not to be a cause. The data of Wynder et al. (see Wynder et al., 1986) have been analysed to prof the null-hypothesis **without** being married **no** pancreatic cancer (conditio sine qua non) relationship. The $\tilde{\chi}^2$ goodness of fit test of a necessary condition relationship is found to be $\tilde{\chi}^2{}_{\text{Calculated}}\,(A_{\text{t}} \leftarrow B_{\text{t}} \mid B) \equiv \frac{c^2}{B} \equiv \frac{11^2}{238} \equiv 0,5084$ which is not significant because it is less than the α = 0.05 critical value for the chi-square distribution (3.841). The $\tilde{\chi}^2$ goodness of fit test of a necessary condition relationship was calculated in the same respect as $\tilde{\chi}^2{}_{\text{Calculated}}\,(A_{\text{t}} \leftarrow B_{\text{t}} \mid \underline{A}) \equiv \frac{c^2}{\underline{A}} \equiv \frac{11^2}{60} \equiv 2,0167$ which is not significant too because it is again less than the α = 0.05 critical value for the chi-square distribution (3.841). To bring it to the point, there is no significant difference between the theoretical distribution of a necessary condition and the observed distribution of a necessary condition. The causal relationship has been found to be $k > 0$ (see Barukčić, 2018d, 2019b, 2019c). Thus far, the data analysed are not self contradictory and do support the null-hypothesis: **without** being married **no** pancreatic cancer. The left-tailed (lt) p Value (Barukčić, 2019d) of the conditio sine qua non relationship has been documented as $pValue_{\text{lt}}\,(A_{\text{t}} \leftarrow B_{\text{t}}) \equiv 1 - e^{-(1-p(A_{\text{t}} \leftarrow B_{\text{t}}))} \equiv 1 - e^{-(c/N)} \equiv 1 - e^{-(11/933)} \equiv 0,0117$ In other words, the null-hypothesis $p\,(A_{\text{t}} \leftarrow B_{\text{t}}) \equiv +1$ cannot be rejected $(pValue \equiv 0,0117)$. Based on the data of the study of Wynder et al. (see Wynder et al., 1986), the conclusion is justified that **without** being married **no** pancreatic cancer $(p\ Value \equiv 0,0117)$.

□

Theorem 3.7 (Without being married no pancreatic cancer II)**.** *Bo et al. (see Bo et al., 2019) investigated the risk factors and the effects of their interactions on pancreatic cancer in a hospital-based case-control study with a sample size of n = 4821. The data of the study of Bo et al. (see Bo et al., 2019) are re-analysed.*

Null hypothesis 3.7. *Being married **is** a necessary condition (conditio sine qua non) of pancreatic cancer. In other words, **without** being married **no** pancreatic cancer.*
A statistical significant difference between an observed (sample) distribution of the conditio sine qua non relationship and the expected distribution of the conditio sine qua non relationship is not given ($\alpha = .05$).

Alternative hypothesis 3.7. *Being married **is not** a necessary condition (conditio sine qua non) of pancreatic cancer.*
A statistical significant difference between an observed (sample) distribution of the conditio sine qua non relationship and the expected distribution of the conditio sine qua non relationship is given ($\alpha = .05$).

Proof by induction (experiment/study). Bo et al. (see Bo et al., 2019) provided data about the relationship between marital status (married, unmarried) and pancreatic cancer. The data available and the statistical analysis of these data are illustrated in detail by table 25.

Tabelle 25: Marital status and pancreatic cancer.

		Pancreatic cancer		
		YES	NO	
Married	YES	1384	2833	4217
	NO	8	596	604
		1392	3429	4821

Causal relationship k =	0,2301
p Value right tailed (HGD) =	0,0000
p (SINE) =	0,9983
$\tilde{\chi}^2$ (SINE | B_t) =	0,0460
$\tilde{\chi}^2$ (SINE | $\underline{A}_t$) =	0,1060
p Value right tailed (HGD) =	0,0000
p Value (SINE) =	0,0017
p (IMP) =	0,4124
$\tilde{\chi}^2$ (IMP | A_t) =	1.903,2224
$\tilde{\chi}^2$ (IMP | $\underline{B}_t$) =	2.340,5917
p Value right tailed (HGD) =	0,0000
p Value (IMP) =	0,4444
p (SINE∩IMP) =	0,4107
$\tilde{\chi}^2$ (SINE∩IMP)$_1$ =	1.903,3284
$\tilde{\chi}^2$ (SINE∩IMP)$_2$ =	2.340,6377
p Value right tailed (HGD) =	0,0000
p Value (SINE∩IMP) =	0,4453
p (EXCL) =	0,7129
$\tilde{\chi}^2$ (EXCL| A_t) =	454,2224
$\tilde{\chi}^2$ (EXCL| B_t) =	1.376,0460
p Value (EXCL) =	0,2495
p(IOI)=	0,5860
p(IOU)=	0,1635

The index of unfairness (see Barukčić, 2019c) of the study of Bo et al. (see Bo et al., 2019), abbreviated as p(IOU), is $p(IOU) \equiv 0,1635$ and is less than 0.3. The data of Bo et al. (see Bo et al., 2019) are not biased and can be used for an analysis of necessary conditions, of sufficient conditions and of necessary and sufficient conditions. The index of independence (see Barukčić, 2019b) of the study of Bo et al. (see Bo et al., 2019), abbreviated as p(IOI), has been calculated as $p(IOI) \equiv 0,5860$ and is greater than 0.3. The data published are potentially biased.

An analysis of an exclusion relationship or of causal relationships k is possible only with some restrictions. The causal relationship k has been calculated as $k = +0,2301$ $(p\ Value\ (HGD)_{\text{right tailed}}\ (X \geq 1384) \equiv 0,0000)$ and is statistically significant. The data of the study of Bo et al. (see Bo et al., 2019) provide evidence of a significant positive causal relationship between marital status (married, unmarried) and pancreatic cancer $(p\ Value\ \equiv 0,0000)$. However, even if the data of Bo et al. (see Bo et al., 2019) support a significant cause-effect relationship between marital status (married, unmarried) and pancreatic cancer, such a significant cause-effect relationship alone is not enough to establish a causal relation between these two factors. Additional information is necessary. Therefore, the data of Bo et al. (see Bo et al., 2019) have been analysed to prof the null-hypothesis **without** being married **no** pancreatic cancer (conditio sine qua non) relationship. The $\tilde{\chi}^2$ goodness of fit test of a necessary condition relationship is found to be $\tilde{\chi}^2{}_{\text{Calculated}}\ (A_{\text{t}} \leftarrow B_{\text{t}} \mid B) \equiv \frac{c^2}{B} \equiv \frac{8^2}{1392} \equiv 0,0460$ which is not significant because it is less than the α = 0.05 critical value for the chi-square distribution (3.841). The $\tilde{\chi}^2$ goodness of fit test of a necessary condition relationship was calculated in the same respect as $\tilde{\chi}^2{}_{\text{Calculated}}\ (A_{\text{t}} \leftarrow B_{\text{t}} \mid \underline{A}) \equiv \frac{c^2}{\underline{A}} \equiv \frac{8^2}{604} \equiv 0,1060$ which is not significant too because it is again less than the α = 0.05 critical value for the chi-square distribution (3.841). In other words, according to the data of Bo et al. (see Bo et al., 2019), there is no significant difference between the theoretical distribution of a necessary condition and the observed distribution of a necessary condition. The causal relationship has been found to be $k > 0$ (see Barukčić, 2018d, 2019b, 2019c). Thus far, the data of Bo et al. (see Bo et al., 2019) are not self contradictory in this context and do support the null-hypothesis: **without** being married **no** pancreatic cancer. The left-tailed (lt) p Value (Barukčić, 2019d) of the conditio sine qua non relationship has been documented as $pValue_{\text{lt}}\ (A_{\text{t}} \leftarrow B_{\text{t}}) \equiv 1 - e^{-(1-p(A_{\text{t}} \leftarrow B_{\text{t}}))} \equiv 1 - e^{-(c/N)} \equiv 1 - e^{-(8/4821)} \equiv 0,0017$. Add it all up, the null-hypothesis $p\ (A_{\text{t}} \leftarrow B_{\text{t}}) \equiv +1$ cannot be rejected $(pValue \equiv 0,0017)$. Based on the data of the study of Bo et al. (see Bo et al., 2019), the conclusion is justified that **without** being married **no** pancreatic cancer $(p\ Value \equiv 0,0017)$.

□

IV. Discussion

Pancreatic cancer with a possible multifactorial etiology is still a completely unresolved issue in human medicine. There have been a few studies of associations between **Helicobacter pylori** infections and pancreatic cancer. Based on the data of Huang et al. (theorem 3.1, table 19), there was not even a minimal evidence of a causal relationship between a Helicobacter pylori infection and pancreatic cancer and we might accept ultimately that a Helicobacter pylori infection and pancreatic cancer are not causally related.

To date, more than 30 epidemiological studies claim that **smoking** (see among other: Bosetti et al., 2012; Kuzmickiene et al., 2013; Parkin et al., 2011) has been definitively identified as being associated with pancreatic cancer. Bosetti et al. (see Bosetti et al., 2012) investigated the dose-response relationship between cigarette smoking and pancreatic cancer too and confirmed that current cigarette smoking is associated with an increased risk of pancreatic cancer while the risk of pancreatic cancer increases with the number of cigarettes smoked and duration of smoking. The results of this study based on the detailed analysis of the data published by Bosetti et al. (see Bosetti et al., 2012) revealed that smoking and pancreatic cancer are independent of each other. Smoking is neither a necessary condition nor a sufficient condition of pancreatic cancer (theorem 3.2, table 20). In other words, a patient can suffer from pancreatic cancer even if a patient never smoked. On the other hand, the relationship if smoking then pancreatic cancer is not true either. There is no causal relationship between smoking and pancreatic cancer. Smoking of cigarettes has nothing to do with pancreatic cancer.

In this context, reports on the relationship between **diabetes mellitus** and pancreatic cancer are inconsistent. The results of this study indicate that diabetes mellitus is not a necessary condition of pancreatic cancer. In other words, the null hypothesis without diabetes mellitus no pancreatic cancer has to be rejected (theorem 3.3, table 21). Consequently, a subject can suffer from pancreatic cancer even if not suffering from diabetes mellitus. This result of this study is not in accordance neither with the results of Huxley et al. (see Huxley et al., 2005), nor with Zhan et al. (see Zhan et al., 2010), nor with Liao et al. (see Liao et al., 2012) nor with the results of other.

Different studies provided some support for the hypothesis that various types of **pancreatitis** itself are associated with pancreatic cancer. A significant conditio per quam relationship and causal relationship between chronic pancreatitis (see Apple et al., 1999; B.-R. Li et al., 2014; Raimondi et al., 2010) and pancreatic cancer has been found in this study (theorem 3.4, table 22) too. Therefore, it cannot be excluded completely, that a chronic pancreatitis is at least a cause of pancreatic cancer. However, the quality of the data analysed may show us this result in a poor light, and we should avoid to conclude that the problem of the etiology of pancreatic cancer is

solved definitely. The justified question is course, why chronic pancreatitis developed in the way the same developed?

Different studies investigated the relationship between **high blood lipid levels** and an increase of the risk of pancreatic cancer but inconsistent results have been reported too. Thiébaut et al. (see Thiébaut et al., 2009) documented an association between intakes of total, saturated, and monounsaturated fat, but not polyunsaturated fat, and pancreatic cancer. In this study, it was demonstrated that hyperlipidemia excludes pancreatic cancer (theorem 3.5, table 23) and vice versa ($p\ Value \equiv 0,0048$). In other words this result means **if hyperlipidemia then no pancreatic cancer** (see example table 3) and equally vice versa. **If pancreatic cancer then no hyperlipidemia** (see example table 4). This outcome really is an amazing result, because the exact mechanism whereby high blood lipid levels could lead to an exclusion of pancreatic cancer is completely unclear. There are several theoretical possibilities to explain the possible role of high blood lipid levels in relation to pancreatic cancer. One possible explanation is that pancreatic cancer may affect mechanically the common bile duct in the head of the pancreas and disturb the fatty acid induced continuous bile excretion The result may be an increased discomfort by an increased bile reflux into the head of the pancreas. Another possible explanation is that a reduced continuous bile excretion caused by pancreatic cancer may reduce the resorption of fatty acids in the intestinal tract which may result in low levels of blood lipids. Currently, most individuals with pancreatic cancer are diagnosed at a late stage when treatment options are limited (see Kenner et al., 2017). An early detection of pancreatic cancer has the potential to provide to substantial improvements in survival. To date, the laboratory analysis of blood lipid levels is quick, extremely easy and and inexpensive. Therefore, it is certainly a logical step to ask, whether the finding of this study if **pancreatic cancer** then **no high blood lipid levels** (lipid lowering drugs considered) could be of any use for screening measures and early detection undertakings of pancreatic cancer.

Traditional views of the family, the family structures and **marriage** often treat the same as a nature given institution. However, family structures, marriage need not bring benefits exclusively. Besides of all, several studies (see X.-D. Wang et al., 2016) reported that marriage is an independent prognostic factor for survival in various cancers including pancreatic cancer. However, this study did not investigate the impact of marital status on the survival of patient with pancreatic cancer. The most noteworthy finding of this study provides evidence of an interaction between **marital status** and pancreatic cancer (see Bo et al., 2019; Wynder et al., 1986). The results of this study show that there is a significant necessary condition relationship between the marital status and pancreatic cancer. Based on the data of Wynder et al. (see Wynder et al., 1986) **without** being married **no** pancreatic cancer ($n = 933; p\ Value \equiv 0,0117$). In addition to this study, based on the data of the study of Bo et al. (see Bo et al., 2019) too, **without** being married **no** pancreatic cancer ($n = 4821; p\ Value \equiv 0,00166$). Indeed, it is all the more astonishing and just quite amazing that marital status (theorem 3.6, table 24) contributes causally (theorem 3.7, table 25) to pancreatic cancer. In the event that the data of the aforementioned studies (see Bo et al., 2019; Wynder et al., 1986) can be reproduced by other studies, further elaboration on these results is needed since this study may be associated with a number of limitations. Due to the case-control study design, the possibility of bias (different definition of marital status bias, recall bias, selection bias et cetera) cannot be completely ruled. Living and cooking together et cetera cannot be considered as the main aspect by which marital status appears to contribute to pancreatic cancer, otherwise, other family members would have to suffer from pancreatic cancer too. Therefore, we should not really be surprised, that in marriage, the physical intimacy of the spouses may be the main path to pancreatic cancer. Even if this fact might seem more remarkable than it actually is, the association between hepatotropic (see Hassan et al., 2008) viruses (Hepatitis B virus (HBV), hepatitis C virus (HCV)) and pancreatic cancer is already discussed in literature. However, the majority of pancreatic tumors are highly malignant adenocarcinomas and occur in the head of the pancreas. In summary, although it seems reasonable to assume that a virus infection may cause pancreatic injuries, to our knowledge, only view authors investigated the possible relationship between human papillomavirus (HPV) and pancreatic (see Tong et al., 2007) neoplasm. Further studies are warranted in this respect. From an epidemiological point of view, we should not be surprised, therefore, if an effective vaccination of the population against human papillomavirus results in a significant reduction of the incidence of pancreatic cancer.

V. Conclusion

Pancreatic cancers are a very heterogeneous group of tumors. With a certain level of safety, this study points out that a viral infection is probably the cause of pancreatic cancer.

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