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# Without oxygen no burning candle

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Received: July 24, 2019; Accepted July 24, 2019; Published: July 24, 2019

### Abstract

**Objective.** Under certain circumstances, the results of multiple investigations – particularly, rigorously-designed trials, can be summarized by systematic reviews and meta-analyses. However, the results of properly conducted meta-analyses can but need not be stronger than single investigations, if (publication) bias is not considered to a necessary extent.

**Methods.** In assessing the significance of publication bias due to study design simple to handle statistical measures for quantifying publication bias are developed and discussed which can be used as a characteristic of a meta-analysis. In addition, these measures may permit comparisons of publication biases between different meta-analyses.

**Results.** Various properties and the performance of the new measures of publication bias are studied and illustrated using simulations and clearly described thought experiments. As a result, individual studies can be reviewed with a higher degree of certainty.

**Conclusions.** Publication bias due to study design is a serious problem in scientific research, which can affect the validity and generalization of conclusions. The index of unfairness and the index of independence are of use to quantify publication bias and to improve the quality of systematic reviews and meta-analyses.

**Keywords:** study design, study type, measuring technique, publication bias

### 1. Introduction

Objective reality is determined by various events too while some of them occur haphazardly, unpredictably, or by chance. In point of fact, our understanding of both chance and randomness, as we ordinarily think of it and its close connection to probability theory open up the possibility to handle both by specific methods in the light of empirical facts. However, relating facts and hypotheses of a particular kind or extrapolating from a possible data set to predictions and general facts is not free of errors (the problem of induction). The data as recordings of events or of observations, called the sample, the sample data and published by a scientific study are more or less only a set of measurements of individuals from a *population*. The sample data actually obtained by a study or an experiment may agree perfectly with the population but the same need not. The quality of sample data has a fundamental impact on the validity of the inferences drawn and how believable a hypothesis is, whether it is justified to rely on the hypothesis in our decisions or not. Various types of study designs in research activity should ensure the most rigorous visibility and discoverability of causal mechanisms too. Thus far, before any statistical analyses of a data set is performed, it is appropriate to provide some evidence whether the data set used is of use at all. With these concerns firmly in mind while adopting a bird's-eye view, the problem of study design with its relation to causal and conditional analysis will be covered by this article.

## 2. Material and Methods

In one way or another, testing hypotheses and theories about the natural world is not completely free of errors. Still, when all goes well, systematic observation and experimentation should assure that different scientists at different times and places are able to generate the same scientific knowledge.

### 2.1 Definitions

#### Definition 2.1.1. (The sample space)

Let the sample space denote a set or a collection of all different possible outcomes of an experiment. Each possible single outcome  $x_t$  of the experiment is said to be a member of the sample space, or to belong to the space  $S(X)$ . A single outcome  $x_t$  of an experiment  $S(X)$  is a member of  $S(X)$  and denoted symbolically by the relation  $x_t \in S(X)$ . A set  $Y$  is contained in another set  $X$  if every element of the set  $Y$  also belongs to the set  $X$ . This relation is expressed symbolically by the expression  $Y \subset X$ , which is the set-theoretic expression for saying that  $Y$  is a subset of  $X$ . A subset of  $X$  that contains no elements is called an empty set, or null set, and it is denoted by the symbol  $\emptyset$ . In a given experiment, a number  $p(x_t)$  is assigned to each event  $x_t$  in the sample space  $S$  which indicates the probability that  $x_t$  will occur. If the event  $x_t$  is certain to occur, then the probability of that event is  $p(x_t)=1$ .

#### Definition 2.1.2. (The 2x2 Table)

A two by two table (also called a contingency table, a notion first used by Karl Pearson (Pearson, 1904) in 1904) is a useful tool for examining relationships between Bernoulli (i. e. Binomial) distributed random variables. Consider the case of a Bernoulli distributed random variable  $A_t$  occurring/existing et cetera with the probability  $p(A_t)$  at the Bernoulli trial (period of time)  $t$ . Furthermore, consider the case of another Bernoulli distributed random variable  $B_t$  occurring/existing et cetera with the probability  $p(B_t)$  at the same Bernoulli trial (period of time)  $t$ . Furthermore, 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)  $t$ . The following table (**Table 1**) may show the relationships in more details.

Table 1. The probabilities of a contingency table

		Conditioned B		
		("Curvature")		
		Yes = +1	No = +0	Total
Condition A	Yes = +1	$p(a_t)$	$p(b_t)$	$p(A_t)$
	No = +0	$p(c_t)$	$p(d_t)$	$p(\underline{A}_t)$
Total		$p(B_t)$	$p(\underline{B}_t)$	1

In this context, it is per definitionem

$$\begin{aligned}
 p(A_t) &\equiv p(a_t) + p(b_t) = 1 - p(\underline{A}_t) \\
 p(B_t) &\equiv p(a_t) + p(c_t) = 1 - p(\underline{B}_t) \\
 p(a_t) &\equiv p(A_t \cap B_t) = 1 - p(b_t) - p(c_t) - p(d_t) \\
 +1 &\equiv p(a_t) + p(b_t) + p(c_t) + p(d_t) \\
 +1 &\equiv p(A_t) + p(\underline{A}_t) = p(B_t) + p(\underline{B}_t) \\
 p(B_t) + p(\Lambda_t) &\equiv p(A_t) = 1 - p(\underline{B}_t) + p(\Lambda_t) \\
 p(\underline{A}_t) &= 1 - (1 - p(\underline{B}_t) + p(\Lambda_t)) = p(\underline{B}_t) - p(\Lambda_t) \\
 p(\Lambda_t) &= p(A_t) - p(B_t) = p(b_t) - p(c_t) \\
 p(b_t) + p(c_t) &= (2 \times p(c_t)) + p(\Lambda_t) = 1 - p(a_t) - p(d_t)
 \end{aligned} \tag{1}$$

while +1 denotes the normalized sample space of  $A_t$  and  $B_t$ . Under conditions of Einstein’s (A. Einstein, 1916) general (I. Barukčić, 2016c, 2016a) theory of relativity,  $\Lambda$  indicates the cosmological “constant” (Albert Einstein, 1917). Einstein’s field equations known as  $R_{\mu\nu} - (R/2)g_{\mu\nu} + \Lambda g_{\mu\nu} = (4 \times 2\pi \times \gamma/c^4) \times T_{\mu\nu}$  can be expressed in terms of probability theory as  $\mathbf{p(B_t)} + \mathbf{p(\Lambda_t)} = \mathbf{1 - p(B_t)} + \mathbf{p(\Lambda_t)} = \mathbf{p(A_t)}$  at each point in space-time  $t$  while  $p(a_t)$ ,  $p(b_t)$ ,  $p(c_t)$  and  $p(d_t)$  may denote the four basic fields of nature. Multiplying by the Ricci tensor  $R_{\mu\nu}$ , we obtain the geometrized form of Einstein’s field equation as  $R_{\mu\nu} - p(B_t) \times R_{\mu\nu} + p(\Lambda_t) \times R_{\mu\nu} = p(A_t) \times R_{\mu\nu}$  where  $p(A_t) \times R_{\mu\nu} = (4 \times 2\pi \times \gamma/c^4) \times T_{\mu\nu}$  and  $p(B_t) \times R_{\mu\nu} = (R/2)g_{\mu\nu}$  and  $\Lambda g_{\mu\nu} = p(\Lambda_t) \times R_{\mu\nu}$ . In this context, a **probability tensor** (I. Barukčić, 2016a) is needed. Under circumstances where the probability of an event is constant from trial to trial (i. e. Binomial distribution), the relationships before simplifies. We obtain some of the relationships *per definitionem*

$$\begin{aligned}
 A &\equiv n \times p(a_t) + n \times p(b_t) = n \times p(A_t) \\
 B &\equiv n \times p(a_t) + n \times p(c_t) = n \times p(B_t) \\
 a &\equiv n \times p(a_t) = n \times p(A_t \cap B_t) \\
 b &\equiv n \times p(b_t) \\
 c &\equiv n \times p(c_t) \\
 d &\equiv n \times p(d_t) \\
 n &\equiv n \times p(a_t) + n \times p(b_t) + n \times p(c_t) + n \times p(d_t) \\
 n &\equiv n \times p(A_t) + n \times p(\underline{A}_t) = n \times p(B_t) + n \times p(\underline{B}_t)
 \end{aligned} \tag{2}$$

The meaning of the abbreviations a, b, c, d, n et cetera are explained by following 2 by 2-table (**Table 2**).

Table 2. The sample space of a contingency table

		Conditioned B		
		(Outcome)		
		Yes = +1	No = +0	Total
Condition A	Yes =+1	a	b	A
	No = +0	c	d	<u>A</u>
Total		B	<u>B</u>	n

**Definition 2.1.3.** (Sufficient condition (*conditio per quam*))

The mathematical formula of the sufficient condition relationship of a population is defined as

$$\begin{aligned}
 p(A_t \rightarrow B_t) &\equiv \frac{(a) + (c) + (d)}{n} = 1 \\
 &\equiv p(a_t) + p(c_t) + p(d_t) \\
 &\equiv p(a_t) + (1 - p(A_t)) \\
 &\equiv (p(B_t) + p(d_t)) \\
 &\equiv +1.
 \end{aligned} \tag{3}$$

**Definition 2.1.4.** (The  $X^2$  Test of Goodness of Fit of a Sufficient Condition)

The chi-square value of a *conditio per quam* relationship using the *continuity correction* (Yates, 1934), is derived (Barukčić, 2018) as

$$X^2((A \rightarrow B)|A) \equiv \frac{((b) - (1/2))^2}{A} + 0 = 0 \tag{4}$$

or alternatively as

$$X^2((A \rightarrow B)|\underline{B}) \equiv \frac{((b) - (1/2))^2}{\underline{B}} + 0 = 0 \tag{5}$$

**Definition 2.1.5.** (Necessary condition (*conditio sine qua non*))

The mathematical formula of the necessary condition relationship of a population is defined as

$$\begin{aligned}
 p(A_t \leftarrow B_t) &\equiv \frac{(a) + (b) + (d)}{n} = 1 \\
 &\equiv p(a_t) + p(b_t) + p(d_t) \\
 &\equiv p(a_t) + (1 - p(B_t)) \\
 &\equiv (p(A_t) + p(d_t)) \\
 &\equiv +1.
 \end{aligned} \tag{6}$$

**Definition 2.1.6.** (The  $X^2$  Test of Goodness of Fit of a Necessary Condition)

Using the continuity correction, the chi-square value of a *conditio sine qua non* distribution follows as

$$X^2 \left( (A \leftarrow B) | B \right) \equiv \frac{\left( (c) - (1/2) \right)^2}{B} + 0 = 0 \quad (7)$$

Depending upon the study design, another method to calculate the chi-square value of a *conditio sine qua non* distribution (while using the continuity correction) is defined as

$$X^2 \left( (A \leftarrow B) | \underline{A} \right) \equiv \frac{\left( (c) - (1/2) \right)^2}{\underline{A}} + 0 = 0 \quad (8)$$

**Definition 2.1.7.** (The exclusion relationship)

The mathematical formula of the exclusion relationship of a population is defined as

$$\begin{aligned} p(A_t | B_t) &\equiv \frac{(c) + (b) + (d)}{n} = 1 \\ &\equiv p(c_t) + p(b_t) + p(d_t) \\ &\equiv p(c_t) + (1 - p(B_t)) \\ &\equiv (1 - p(A_t) + p(b_t)) \\ &\equiv +1. \end{aligned} \quad (9)$$

**Definition 2.1.8.** (The  $X^2$  Test of Goodness of Fit of the Exclusion Relationship)

The chi square value with degree of freedom  $2-1=1$  of the exclusion relationship (Barukčić, 1989; Barukčić, 1997; Barukčić, 2005; Barukčić, 2006; Barukčić, 2009; Barukčić, 2011; Barukčić, 2012; Barukčić, 2016; Barukčić, 2017; Barukčić, 2018) *with a continuity correction* can be calculated as

$$X^2 \left( (A | B) | A \right) \equiv \frac{\left( (a) - (1/2) \right)^2}{A} + 0 = 0 \quad (10)$$

Depending upon the study design, another method to calculate the chi-square value **of the exclusion relationship** is defined as

$$X^2 \left( (A | B) | B \right) \equiv \frac{\left( (a) - (1/2) \right)^2}{B} + 0 = 0 \quad (11)$$

The chi square Goodness of Fit Test of the exclusion relationship examines how well observed data compare with the expected theoretical distribution of an exclusion relationship.

**Definition 2.1.9.** (Necessary and sufficient condition)

The mathematical formula of the necessary and sufficient condition relationship of a population is defined as

$$\begin{aligned}
 p(A_t \leftrightarrow B_t) &\equiv \frac{(a_t) + (d_t)}{n} = 1 \\
 &\equiv p(a_t) + p(d_t) \\
 &\equiv (p(A_t) - p(b_t)) + ((1 - p(A_t)) - p(c_t)) \\
 &\equiv (1 - p(b_t) - p(c_t)) \\
 &\equiv +1.
 \end{aligned} \tag{12}$$

**Definition 2.1.10.** (The  $X^2$  Test of Goodness of Fit of the necessary and sufficient condition)

Using the continuity correction, the chi-square value of the necessary and sufficient condition can be calculated as

$$X^2(A \leftrightarrow B) \equiv \frac{((c_t) - (1/2))^2}{B} + \frac{((b_t) - (1/2))^2}{\underline{B}} = 0 \tag{13}$$

The chi-square value of the necessary and sufficient condition distribution (while using the continuity correction) be defined as

$$X^2(A \leftrightarrow B) \equiv \frac{((c_t) - (1/2))^2}{A} + \frac{((b_t) - (1/2))^2}{\underline{A}} = 0 \tag{14}$$

**Definition 2.1.11.** (Either  $A_t$  or  $B_t$  relationship)

The mathematical formula of the either  $A_t$  or  $B_t$  relationship of a population is defined as

$$\begin{aligned}
 p(A_t > - < B_t) &\equiv \frac{(b_t) + (c_t)}{n} = 1 \\
 &\equiv p(b_t) + p(c_t) \\
 &\equiv (p(A_t) - p(a_t)) + ((1 - p(A_t)) - p(d_t)) \\
 &\equiv (1 - p(a_t) - p(d_t)) \\
 &\equiv +1.
 \end{aligned} \tag{15}$$

**Definition 2.1.12.** (The  $X^2$  Test of Goodness of Fit of the *either*  $A_t$  or  $B_t$  relationship)

Using the continuity correction, the chi-square value of the *either*  $A_t$  or  $B_t$  relationship can be defined as

$$X^2(A > - < B) \equiv \frac{\left((a) - (1/2)\right)^2}{B} + \frac{\left((d) - (1/2)\right)^2}{\underline{B}} = 0 \quad (16)$$

Another method to calculate the chi-square value of the *either*  $A_t$  or  $B_t$  relationship (while using the continuity correction) can be defined as

$$X^2(A > - < B) \equiv \frac{\left((a) - (1/2)\right)^2}{A} + \frac{\left((d) - (1/2)\right)^2}{\underline{A}} = 0 \quad (17)$$

**Definition 2.1.13.** (The Chi-square goodness-of fit test for a single patient)

The Chi-Square goodness-of fit test as proposed by Karl Pearson (Pearson, 1900) is of use in our everyday life too. Thus far, let  $x_t$  denote the value of a random variable  $X$  at a certain point in space-time  $t$ . Let us determine the value of the same random variable  $X$  under identical conditions some time later i. e. at the point in space-time  $t+1$ . Has there been any significant change of the value of a random variable from  $t$  to  $t+1$ ? The chi-square goodness of fit test can be applied to determine whether (sample distribution) data observed are consistent with (theoretical distribution) hypothesized data. The degrees of freedom (d.f.) of a chi-square goodness of fit test is equal to the number of levels ( $k$ ) of the categorical variable minus 1, in this case  $d.f. = 2-1 = 1$ . In general, the chi-square goodness of fit test is given by

$$X_{Calculated}^2 \equiv \frac{\left((x_{t+1}) - (x_t)\right)^2}{(x_t)} + \frac{\left((x_t) - (x_t)\right)^2}{(x_t)} = \frac{\left((x_{t+1}) - (x_t)\right)^2}{(x_t)} + 0 = 0 \quad (18)$$

*Example.*

An Epstein-Barr virus (EBV) infection can be monitored to some extent by immunoglobulin G (IgG) antibodies to EBV viral capsid antigens (VCA). A physician is prescribing a drug regimen to cure an EBV infection and tries to get some evidence ( $\alpha = .0455$ ) whether the drugs prescribed are of any use. The EBV VCA IgG titer before the therapy was 100 I.E./ml. ( $t=1$ ). After three months of therapy, the EBV titer declined to 50 I.E./ml. Is the therapy of any use? The  $X^2$  critical at  $\alpha = .0455$  is  $X^2$  (critical) = 4. Thus far, if the  $X^2$  (calculated) is greater than 4, there is some evidence that the therapy is of help, even if one single patient is regarded. We obtain the following result.

$$X_{Calculated}^2 \equiv \frac{\left((x_{t+1}) - (x_t)\right)^2}{(x_t)} = \frac{\left((100) - (50)\right)^2}{(50)} = \frac{(2500)}{(50)} + 0 = 50 \quad (19)$$

Conclusion. The therapy prescribed is of help.

**Definition 2.1.14.** (Independence)

In the case of independence (Moivre, 1718), (Kolmogoroff, 1933) of  $A_t$  and  $B_t$  it is generally valid that

$$p(A_t \cap B_t) \equiv p(A_t) \times p(B_t) \quad (20)$$

**Definition 2.1.15.** (The Mathematical Formula of the Causal Relationship  $k$ )

The mathematical formula of the causal relationship  $k$  (I. Barukčić, 1989), (I. Barukčić, 2016b), (I. Barukčić, 2017), (I. Barukčić, 2018b), (I. Barukčić, 2018d), (I. Barukčić, 2018c), (I. Barukčić, 2011), (I. Barukčić, 2018a), (K. Barukčić, Barukčić, & Barukčić, 2018) is defined at every single event, at every single Bernoulli trial  $t$ , as

$$k(A_t, B_t) \equiv \frac{p(A_t \cap B_t) - (p(A_t) \times p(B_t))}{\sqrt{p(A_t) \times (1 - p(A_t)) \times p(B_t) \times (1 - p(B_t))}} \quad (21)$$

where  $A_t$  denotes the cause and  $B_t$  denotes the effect. Under some certain circumstances, the chi-square distribution can be applied to determine the significance of causal relationship  $k$ . Again, it necessary to point out that neither Pearson's concept of correlation nor Pearson's concept of  $\phi$  is identical with causation. The mathematical formula of the causal relationship  $k$  has nothing to do with Pearson's methods and is not identical with correlation. This has been proved many times and is widely discussed in many publications.

**Definition 2.1.16.** (The 95% Confidence Interval of the Causal Relationship  $k$ )

The 95% interval for the causal relationship  $k$  was calculated by the formula

$$\left\{ k(A_t, B_t) - \sqrt{\frac{5}{n}} ; k(A_t, B_t) + \sqrt{\frac{5}{n}} \right\} \quad (22)$$

**Definition 2.1.17.** (Index of unfairness)

The index of unfairness (IOU) is defined as

$$IOU \equiv \left( \left( \frac{A + B}{n} \right) - 1 \right) \quad (23)$$

The range of  $A$  is  $0 \leq A \leq n$ , while the range of  $B$  is  $0 \leq B \leq n$ . A study design based on  $A=B=0$  leads to an index of unfairness of  $IOU = (((0+0)/n)-1) = -1$ . A study design which demands that  $A=B=n$  leads to an index of unfairness of  $IOU = (((n+n)/n)-1) = +1$ . In particular, the range of the index of unfairness is  $[-1; +1]$ . In this context let us define the following.

**Definition 2.1.18.** (The probability of an index of unfairness)

The probability of an unfairness  $p(IOU)$  is defined as

$$p(IOU) \equiv \text{Absolute} \left( \left( \frac{A + B}{n} \right) - 1 \right) \quad (24)$$



**Definition 2.1.19.** Index of independence (IOI)

The index of independence (IOI) is defined as

$$IOI \equiv \left( \left( \frac{A + B}{n} \right) - 1 \right) \quad (25)$$

**Definition 2.1.20.** (The probability of an index of independence)

The probability of an index of independence  $p(IOI)$  is defined as

$$p(IOI) \equiv \text{Absolute} \left( \left( \frac{A + B}{n} \right) - 1 \right) \quad (26)$$

**2.2 Material****Experiment 2.2.1.** (Hot plate experiment)

Research on human participants requires protection at least according to the Declaration of Helsinki issued by the World Medical Association (Declaration of Helsinki, 1997). Among other clearly formulated experimental protocols should be approved by independent ethical review boards (ethics committees and institutional review boards). The following experiment is only a thought experiment and there is no need for such an approval. Let  $A_i$  denote a plate, a Binomial random variable, which can take only two values, *either* hot = +1 *or* not hot = +0. A hot plate is defined by the fact that the same damages a finger of a human being in a certain way without any hesitation. One property of a cold plate is that the same does not damage the finger of a human being in a certain way. Let  $B_i$  denote an index finger of a human being, a Binomial random variable, which can take only two values, *either* injured = +1 *or* not injured = +0. Inclusion and exclusion criteria are defined. A placebo group is completely identical with the verum group. The experiments are independent and performed under the same conditions et cetera.

**Experiment 2.2.2.** (Burning candle experiment)

Let  $A_i$  denote gaseous oxygen, a Binomial random variable, which can take only two values, *either* gaseous oxygen present = +1 *or* not gaseous oxygen not present = +0. Gaseous oxygen present means that the amount is enough to assure that a candle can burn. Let  $B_i$  denote a candle, a Binomial random variable, which can take only two values, *either* a candle is burning = +1 *or* a candle is not burning = +0.

### 3. Results

#### Theorem 3.1. (Study design and the causal relationship k)

Several experiments with different study design were performed. The following data were obtained and are presented by the following 2 by 2-tables (**Table 3**, **Table 4**, **Table 5**). A very fair experiment is illustrated by the Table 3.

Table 3. The relationship between a plate and a finger

		Finger injured		Total
		Yes = +1	No = +0	
Hot Plate	Yes =+1	50	0	50
	No = +0	0	50	50
Total		50	50	100

An extremely unfair experiment is illustrated by table 4.

Table 4. The relationship between a plate and a finger

		Finger injured		Total
		Yes = +1	No = +0	
Hot Plate	Yes =+1	1	0	1
	No = +0	0	99	99
Total		1	99	100

Another extremely unfair experiment is illustrated by table 5.

Table 5. The relationship between a plate and a finger

		Finger injured		Total
		Yes = +1	No = +0	
Hot Plate	Yes =+1	99	0	99
	No = +0	0	1	1
Total		99	1	100

#### Claim.

A  $p(\text{IOU})=p(\text{IOI})=0$  assures the recognition of causal relationships.

**Proof.**

The data above are tested for significance. The data of the table 3 are analyzed and presented by table 5. The data of the table 4 are analyzed and presented by table 6. The data of the table 5 are analyzed and presented by table 7.

Table 5. The statistical analysis of the data of table 3.

	<b>p(IOU) = 0,000</b>	<b>p(IOI) = 0,000</b>
$k = +1$		
P value (k   HGD) = 9,9117E-30	Chi Sq.(k) = 100,000	
p (SINE) = 1	Chi Sq. 1(SINE) = 0,000	Chi Sq. 2(SINE) = 0,000
p (IMP) = 1	Chi Sq. 1(IMP) = 0,000	Chi Sq. 2(IMP) = 0,000
p (EXCL) = 0,5	Chi Sq. 1(EXCL) = 50,000	Chi Sq. 2(EXCL) = 50,000

The data as provided by table 4 are extremely unfair.

Table 6. The statistical analysis of the data of table 4.

	<b>p(IOU) = 0,980</b>	<b>p(IOI) = 0,000</b>
$k = +1$		
P value (k   HGD) = 0,01	Chi Sq.(k) = 100,000	
p (SINE) = 1	Chi Sq. 1(SINE) = 0,000	Chi Sq. 2(SINE) = 0,000
p (IMP) = 1	Chi Sq. 1(IMP) = 0,000	Chi Sq. 2(IMP) = 0,000
p (EXCL) = 0,99	<b>Chi Sq. 1(EXCL) = 1,000</b>	<b>Chi Sq. 2(EXCL) = 1,000</b>

Due to the study design, the data as provided by table 5 are extremely unfair too.

Table 7. The statistical analysis of the data of table 5.

	<b>p(IOU) = 0,980</b>	<b>p(IOI) = 0,000</b>
$k = +1$		
P value (k   HGD) = 0,01	Chi Sq.(k) = 100,000	
p (SINE) = 1	Chi Sq. 1(SINE) = 0,000	Chi Sq. 2(SINE) = 0,000
p (IMP) = 1	Chi Sq. 1(IMP) = 0,000	Chi Sq. 2(IMP) = 0,000
p (EXCL) = 0,99	<b>Chi Sq. 1(EXCL) = 99,000</b>	<b>Chi Sq. 2(EXCL) = 99,000</b>

The results as presented by Table 5 are self-evident. The causal relationship  $k=+1$ , the P value calculated according to the hypergeometric distribution is P value = 9,9117E-30, **p (IOU) = p (IOI) = 0**. The necessary condition is given (Chi Sq. 1(SINE) = 0,000; Chi Sq. 2(SINE) = 0,000) and at the same time, the sufficient condition is given (Chi Sq. 1(IMP)=0,000; Chi Sq. 2(IMP) = 0,000) too. A perfect study design should assure as much as possible an  $p(\text{IOU}) = p(\text{IOI})$  equal or very near to zero. As we can see, *a significant causal relationship alone without an evidence of a significant conditio sine qua non relationship or a significant conditio per quam relationship or a significant exclusion relationship et cetera indicates to biased data* and not that much to a secured finding. However, the motivation of a researcher and other factors can influence the study design with the consequence that even contradictory data can be achieved. (Table 6). The index of unfairness is extremely unfair with  $p(\text{IOU}) = 0,98$  while  $p(\text{IOI}) = 0$ . Even under these very extreme conditions, theoretically, it is possible to recognize a causal relationship ( $k=+1$ , P value = 0,01). The necessary condition is given (Chi Sq. 1(SINE) = 0,000; Chi Sq.

2(SINE) = 0,000) and at the same time, the sufficient condition is given (Chi Sq. 1(IMP)=0,000; Chi Sq. 2(IMP) = 0,000) too. In particular, the exclusion relationship is significant too (Chi Sq. 1(EXCL) = 1,000; Chi Sq. 2(EXCL) = 1,000) which is a contradiction. Logically, it is not possible, that  $A_t$  excludes  $B_t$  and vice versa and that equally  $A_t$  is a necessary condition of  $B_t$ . A  $p(\text{IOU})$  which is much greater than  $p(\text{IOI})$  can imply contradictions. In such cases, the use of the causal relationship is of help. A causal relationship which is greater 0 excludes a significant exclusion relationship. The reason is that in the case of an exclusion relationship  $p(a_t) = p(A_t \cap B_t) = 0$  and the causal relationship  $k$  derived at every single event, at every single Bernoulli trial  $t$ , as

$$k(A_t, B_t) \equiv \frac{p(A_t \cap B_t) - (p(A_t) \times p(B_t))}{\sqrt{p(A_t) \times (1 - p(A_t)) \times p(B_t) \times (1 - p(B_t))}} \quad (27)$$

where  $A_t$  denotes the cause and  $B_t$  denotes the effect and reduces under these circumstances to

$$k(A_t, B_t) \equiv \frac{0 - (p(A_t) \times p(B_t))}{\sqrt{p(A_t) \times (1 - p(A_t)) \times p(B_t) \times (1 - p(B_t))}} < 0 \quad (28)$$

A significant exclusion relationship demands a negative causal relationship  $k$ . Another way to circumvent problems like these is to assure a study design where  $a = d$ .

**Quod erat demonstrandum.**

**Theorem 3.2.** (Biased data and the causal relationship k)

The experiments of theorem 3.1 were performed under ideal conditions. In real life bias of different kind must be considered. We analyze the same relationship with data which are biased due to several causes. The following data which are biased were obtained and are presented by the following 2 by 2-tables (**Table 8**, **Table 9**, **Table 10**). A very fair experiment is illustrated by the Table 8.

Table 8. The relationship between a plate and a finger

		Finger injured		
		Yes = +1	No = +0	Total
Hot Plate	Yes =+1	1	0	1
	No = +0	49	50	99
Total		50	50	100

An extremely unfair experiment is illustrated by table 9 too.

Table 9. The relationship between a plate and a finger

		Finger injured		
		Yes = +1	No = +0	Total
Hot Plate	Yes =+1	49	49	98
	No = +0	1	1	2
Total		50	50	100

Another extremely biased experiment is illustrated by table 10.

Table 10. The relationship between a plate and a finger

		Finger injured		
		Yes = +1	No = +0	Total
Hot Plate	Yes =+1	5	5	10
	No = +0	135	5	140
Total		140	10	150

**Claim.**

A high  $p(\text{IOU})$  and a high  $p(\text{IOI})$  need not to exclude the recognition of conditions. A  $p(\text{IOI}) < 0,5$  appears to enable the recognition of causal relationships while an  $p(\text{IOI}) < 0,25$  is of great help in analysing causal data. The higher  $p(\text{IOI})$  the less are the data suitable for causal analysis.

**Proof.**

The data are tested again for significance. The statistical analysis of the data of the table 8 is presented by table 11.

Table 11. The statistical analysis of the data of table 8.

	<b>p(IOU) = 0,490</b>	<b>p(IOI) = 0,490</b>
<b>k = +0,10050378</b>		
<b>P value (k   HGD) = 0,5</b>	Chi Sq.(k) = 1,010	
p (SINE) = 0,51	Chi Sq. 1(SINE) = 48,020	Chi Sq. 2(SINE) = 24,253
p (IMP) = 1	<b>Chi Sq. 1(IMP) = 0,000</b>	<b>Chi Sq. 2(IMP) = 0,000</b>
p (EXCL) = 0,99	<b>Chi Sq. 1(EXCL) = 0,020</b>	<b>Chi Sq. 2(EXCL) = 1,000</b>

We are reanalyzing a secured causal relationship between a hot plate and an injured human finger. However, a study design lead to data which are biased and only of limited value. The study of Table 8 has an **p(IOU) = p(IOI) = 0,49** but we have not been able to recognize a significant causal relationship ( $k=+0,101$ ; P value = 0,5) even if a causal relationship in the population between a hot plate and an injured human finger is given. Thus far, it is not enough that  $p(\text{IOU}) = p(\text{IOI})$  to be able to consider data for a causal analysis. The study design should assure that both,  $p(\text{IOU})$  and  $p(\text{IOI})$ , should be as near as possible to zero. Briefly, that the data are biased can be recognized by the fact that both is significant, the *conditio per quam* (Chi Sq. 1(IMP) = 0,000; Chi Sq. 2(IMP) = 0,000) and the exclusion relationship (Chi Sq. 1(EXCL) = 0,020; Chi Sq. 2(EXCL) = 1,000). This is a contradiction, which just don't know what is correct. Such data cannot be considered for a statistical analysis or the causal relationship  $k$  must decide what is correct or what could be correct. *A significant conditio per quam relationship demands a positive causal relationship k*. In other words, if such data should be used for further analysis, we should conclude due to preliminary reasons that there is a significant *conditio per quam* relationship and not a significant exclusion relationship. However, a high  $p(\text{IOU})$  and a high  $p(\text{IOI})$  indicates potentially biased data. In this context, the statistical analysis of the data of the table 9 is presented by table 12.

Table 12. The statistical analysis of the data of table 9.

	<b>p(IOU) = 0,480</b>	<b>p(IOI) = 0,480</b>
<b>k = 0,000</b>		
<b>P value (k   HGD) = 0,505</b>	Chi Sq.(k) = 0,000	
p (SINE) = 0,990	<b>Chi Sq. 1(SINE) = 0,020</b>	<b>Chi Sq. 2(SINE) = 0,500</b>
p (IMP) = 0,510	Chi Sq. 1(IMP) = 48,020	Chi Sq. 2(IMP) = 24,500
p (EXCL) = 0,510	Chi Sq. 1(EXCL) = 48,020	Chi Sq. 2(EXCL) = 24,500

The causal relationship between a hot plate and an injured human finger is secured and clear. Still, if we rely on the data of the study above (Table 9) there is no causal relationship between a hot plate and an injured human finger ( $k = +0$ ; P value = 0,505). The conclusion cannot be that we are just not able to recognize causal relationships by statistical methods. Among other, the study design technology must be improved to ensure the quality of data. *A high p(IOU) and a high p(IOI) may exclude the recognition of causal relationships but not the recognition of conditions too*. Even under these very unfair conditions it was possible to recognize that there is a significant *conditio sine qua non* relationship. Extremely biased data are presented by table 10. The statistical analysis of the same data is presented by table 13.

Table 13. The statistical analysis of the data of table 10.

	$p(\text{IOU}) = 0,000$	$p(\text{IOI}) = 0,867$
$k = -0,464$		
$P \text{ value } (k   \text{HGD}) = 0,000$	Chi Sq.(k) = 32,334	
$p(\text{SINE}) = 0,100$	Chi Sq. 1(SINE) = 130,179	Chi Sq. 2(SINE) = 130,179
$p(\text{IMP}) = 0,967$	Chi Sq. 1(IMP) = 2,500	Chi Sq. 2(IMP) = 2,500
$p(\text{SINE} \wedge \text{IMP}) = 0,067$	Chi Sq. 1(SINE $\wedge$ IMP) = 132,679	Chi Sq. 1(SINE $\wedge$ IMP) = 132,679
$p(\text{EXCL}) = 0,967$	Chi Sq. 1(EXCL) = 0,179	Chi Sq. 2(EXCL) = 2,500

Table 10 presents data of a secured relationship between a hot plate and an injured human finger. Due to several factors, studies may produce biased data with the consequence that the same are only of very limited or of none value. This is demonstrated by the statistical analysis (Table 13) of the data of table 10. The data published support the position that there is a highly significant negative causal relationship between a hot plate and an injured human finger ( $k = -0,464$ ;  $P \text{ value} = 0,000$ ) while at the same time the exclusion relationship ( $\text{Chi Sq. 1}(\text{EXCL}) = 0,179$ ;  $\text{Chi Sq. 2}(\text{EXCL}) = 2,500$ ) is significant too. We would have to recognize: A hot plate prevents from an injured human finger. Such a conclusion is not completely illogical. Human subject have a free will and do know that a hot plate can damage the finger. Therefore, the most refused to put their own finger on a hot plate. Only 5/10 had the courage to put their finger on a hot plate. In toto 135/140 had an injured finger but not due to a hot plate. The data above are self-contradictory. The *conditio sine qua non* relationship ( $p(\text{IMP}) = 0,967$ ;  $\text{Chi Sq. 1}(\text{IMP}) = 2,500$ ;  $\text{Chi Sq. 2}(\text{IMP}) = 2,500$ ) was significant too. *The  $p(\text{IOU}) = 0$  indicates that the analysis of conditions is possible.* Contrary to expectation,  $p(\text{IOI}) = 0,867$  indicates that the analysis of causal relationships does not make any sense because it cannot be excluded that the data are biased too much. Due to the self-contradictory data, we just cannot decide what is true and what is not true. Such data should be excluded from analysis until a more precise technology is known how to deal with such kind of data.

A  $p(\text{IOI}) < 0,5$  appears to enable the recognition of causal relationships while an  $p(\text{IOI}) < 0,25$  is of great help in analysing causal data. The higher  $p(\text{IOI})$  the less are the data suitable for causal analysis.

**Quod erat demonstrandum.**

**Theorem 3.3.** (*Without oxygen no burning candle*)

The relationship between the behavior of a candle produced out of wax and oxygen is studied. The investigator lights the candle wick of many candles (old, you, big, small, red, green, curved, straight et cetera) under different conditions. Candle flame reacts with oxygen such that heat and light which characterizes a candle are produced. The *verum group* is studied under conditions of the air we breathe, i. e. about 21 percent oxygen. The placebo group is studied under conditions where no oxygen present. Fire itself needs at least 16 percent oxygen. Below that the fire will go out. In the following, a burning candle is enclosed and hermetically sealed by an appropriate cup of glass while the concentration of oxygen inside this enclosed small space is measured. When all oxygen is consumed, it is recorded whether the candle is burning or not (**case d**). Different studies provided different data (Table 14, Table 15, Table 16).

Table 14. Oxygen and a burning candle

		Burning candle		
		Yes = +1	No = +0	Total
Oxygen	Yes =+1	25	50	75
	No = +0	0	25	25
Total		25	75	100

The data of Table 14 are analyzed by table 17.

Table 15. Oxygen and a burning candle

		Burning candle		
		Yes = +1	No = +0	Total
Oxygen	Yes =+1	90	5	95
	No = +0	0	5	5
Total		90	10	100

The data of Table 15 are analyzed by table 18.

Table 16. Oxygen and a burning candle

		Burning candle		
		Yes = +1	No = +0	Total
Oxygen	Yes =+1	25	50	75
	No = +0	0	25	25
Total		25	75	100

The data of Table 16 are analyzed by table 19.



**Claim.**

The decision whether data are biased with respect to statistical analysis of conditions is supported by *the index of unfairness*.

**Proof.**

Different aspects of the relationship between oxygen and a burning candle are pictured by several studies. The data of Table 14 are analyzed by table 17.

Table 17. The statistical analysis of the data of table 14.

	<b>p(IOU) = 0,000</b>	<b>p(IOI) = 0,500</b>
<b>k = 0,333</b>		
<b>P value (k   HGD) = 0,000</b>	Chi Sq.(k) = 11,111	
<b>p (SINE) = 1,000</b>	<b>Chi Sq. 1(SINE) = 0,000</b>	<b>Chi Sq. 2(SINE) = 0,000</b>
p (IMP) = 0,500	Chi Sq. 1(IMP) = 33,333	Chi Sq. 2(IMP) = 33,333
p (SINE ^ IMP) = 0,500	Chi Sq. 1(SINE ^ IMP) = 33,333	Chi Sq. 1(SINE ^ IMP) = 33,333
p (EXCL) = 0,750	Chi Sq. 1(EXCL) = 25,000	Chi Sq. 2(EXCL) = 8,333

In our everyday life, the relationship between oxygen and a burning candle is clear: *without oxygen no burning candle*. In particular, oxygen itself is by far not the cause of a burning candle. However, the data of the study analyzed are to some extent self-contradictory. The study design is based on the assumption that  $(a = 25) = (d=25)$  and yielded an **p(IOU) = 0**. As a consequence, it was possible to analyze the data for conditions (i.e risk factors). We were able to recognize: *without oxygen no burning candle* ( $p(\text{SINE}) = 1,000$ ; Chi Sq. 1(SINE) = 0,000; Chi Sq. 2(SINE) = 0,000). However, the same study supports the hypothesis of a highly significant cause effect relationship between oxygen and a burning candle ( $k = +0,333$ ; P value (k|HGD) = 0,000). Such a conclusion appears not to be justified. With respect to causal analysis it cannot be excluded that study is biased ( $p(\text{IOI}) = 0,5$ ). Furthermore, *neither* the study analyzed *nor* another study has been able to provide reproduceable evidence of condition per quam relationship ( $p(\text{IMP}) = 0,500$ ; Chi Sq. 1(IMP) = 33,333; Chi Sq. 2(IMP) = 33,333) between oxygen and a burning candle (i.e. *if oxygen then burning candle*). A high  $p(\text{IOI})$  need not to exclude the analysis of the data for conditions (i.e. risk factors). More fundamentally, it is important to take great care about *the index of independence* (IOI) when data are considered for causal analysis. Even if the data support the hypothesis of a highly significant causal relationship, it is important to stress here that these data should not be used for that purposes. As next, the data of another study (Table 15) are analyzed by table 18.

Table 18. The statistical analysis of the data of table 15.

	<b>p(IOU) = 0,850</b>	<b>p(IOI) = 0,050</b>
<b>k = +0,688</b>		
<b>P value (k   HGD) = 0,000</b>	Chi Sq.(k) = 11,111	
<b>p (SINE) = 1,000</b>	<b>Chi Sq. 1(SINE) = 0,000</b>	<b>Chi Sq. 2(SINE) = 0,000</b>
p (IMP) = 0,950	Chi Sq. 1(IMP) = 2,500	Chi Sq. 2(IMP) = 0,263
p (SINE ^ IMP) = 0,950	Chi Sq. 1(SINE ^ IMP) = 2,500	Chi Sq. 1(SINE ^ IMP) = 0,263
p (EXCL) = 0,100	Chi Sq. 1(EXCL) = 90,000	Chi Sq. 2(EXCL) = 85,263

To be sure, we can state that the data (Table 15) support the hypotheses: *without oxygen no burning candle* ( $p(\text{SINE}) = 1,000$ ; Chi Sq. 1(SINE) = 0,000; Chi Sq. 2(SINE) = 0,000) even if  $p(\text{IOU}) = 0,85$ . However, the

problem with these data is that a significant causal relationship ( $k=+0,688$ ; P value ( $k | HGD$ ) = 0,000) is supported too, that a significant conditio per quam relationship ( $p(IMP) = 0,950$ ; Chi Sq. 1(IMP) = 2,500; Chi Sq. 2(IMP) = 0,263) is supported too and that a significant necessary and sufficient condition ( $p(SINE \wedge IMP) = 0,950$ ; Chi Sq. 1(SINE  $\wedge$  IMP) = 2,500; Chi Sq. 1(SINE  $\wedge$  IMP) = 0,263) is supported too. In this case, the problem can be solved quickly. Oxygen is not the cause of a burning candle, even if  $p(IOI)$  is very low ( $p(IOI)=0,05$ ). However, in most cases an investigator faced with an unknown situation and needs reliable methods which are of help to decide whether the data analyzed are worth being analyzed or not. In toto, it is not enough to rely only on statistical measures. The quality of data fundamentally determined by study design and other factors must be considered too. The statistical analysis (Table 18) of the data of table 15 is of only limited value. We just cannot decide what is true and what is not true. A high  $p(IOU)$  can be associated with bias and the data should be analyzed only with very great care or not at all.

#### Quod erat demonstrandum.

#### 4. Discussion

Kicinski et al. (Kicinski, Springate, & Kontopantelis, 2015) and other investigated publication bias in meta-analyses and were able to find evidence of publication bias in systematic reviews. The application of appropriate statistical methods in biomedical research alone on data collected from clinical trials and other studies is not enough and does not guarantee conclusions which are valid and reproduceable. The use of funnel plot's (Light & Pillemer, 1984) is one way to detect publication bias in an examination. Other formal tests for publication bias were developed by Begg and Mazumdar (Begg & Mazumdar, 1994) and by Egger et al. (Egger, Smith, Schneider, & Minder, 1997). Higgins et al. (Higgins & Thompson, 2002) developed a statistical tool to measure the extent of heterogeneity in a meta-analysis. In a slightly different way, the development and the use of other effective measures to reduce publication bias in clinical trials and other studies is necessary too and justified. The analysis of data for causal relationships is not without problems but not impossible. However, bias in this context may invalidate the conclusions drawn. Therefore, as a rule of thumb, for causal analysis, a study design should assure as much as possible that

$$p(IOU) + p(IOI) < 0,5 \quad (29)$$

The following table (Table 19) may provide a useful overview on this relationship.

Table 19. The relationship between  $p(IOU)$  and  $p(IOI)$

		p(IOI)		Total
		< 0,5	≥ 0,5	
p(IOU)	< 0,5	Causal analysis	Analysis of conditions	
	≥ 0,5	Analysis of conditions, with great care!	No analysis. Data are potentially biased.	
Total				1

A very low  $p(IOI)$  is not necessary to recognize conditions. However, a very high  $p(IOI)$  can indicate extremely biased data and the conclusions drawn could be potentially invalid. Even if  $p(IOU)$  is very low, data with a  $p(IOI)$  beyond 0,75 are of very limited value even for the for the analysis of conditions.

#### 5. Conclusion

The impact of bias on statistical analysis of data can be reduced by an appropriate study design. Ex post, the index of unfairness (IOU) and the index of independence (IOI) are of use to reduce publication bias.

### Financial support and sponsorship

Nil.

### Conflict of interest statement

The authors declare that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

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