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Atorvastatin does not protect against acute myocardial infarction

Research article

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Abstract

Background:

Today, statins are the first-choice agents for reducing high blood cholesterol in people with and without a past history of coronary artery disease (CAD).

Methods:

Studies which investigated the relationship between statins and coronary events were considered for reanalysis.

Results:

The contradictions regarding statins are apparent. Some studies show presumed positive effects with respect ot coronary events while other studies do not comply.

Conclusion:

Statins do not help with the required reliability against coronary events.

Keywords: Atorvastatin; Coronary events; Cause; Effect; Causal relationship k; Causality; Causation

1. Introduction

High lipid levels are repeatedly accused as so called risk factors for atherosclerotic cardiovascular events. However, what is the truth and what is pure fiction? Is there anything at all [1] in this respect that we may regard as certain (the lipid paradox)? Anderson et al. published 1987 a 30-year follow-up of the Framingham Heart Study [2] and found that there is "... a direct association between falling cholesterol levels ... and ... death rate increase ..."[3] Al-Mallah et al. found that "... lower LDL-cholesterol at admission was associated with decreased 3-year survival in patients with NSTEMI."[4] Several other reports described similar paradoxical results. Cho et al. found "... months after PCI ... better results

[1] Nilsson G, Leppert J, Ohrvik J. Enigma of the cholesterol paradox in acute myocardial infarction: lessons from an 8-year follow-up of all-cause mortality in an age-matched and sex-matched case-control study with controls from the patients' recruitment area. BMJ Open. 2022 Jul 27;12(7):e057562. doi: 10.1136/bmjopen-2021-057562. PMID: 35896296; PMCID: PMC9335044.

[2] Mahmood SS, Levy D, Vasan RS, Wang TJ. The Framingham Heart Study and the epidemiology of cardiovascular disease: a historical perspective. Lancet. 2014 Mar 15;383(9921):999-1008. doi: 10.1016/S0140-6736(13)61752-3. Epub 2013 Sep 29. PMID: 24084292; PMCID: PMC4159698.

[3] Anderson KM, Castelli WP, Levy D. Cholesterol and mortality. 30 years of follow-up from the Framingham study. JAMA. 1987 Apr 24;257(16):2176-80. doi: 10.1001/jama.257.16.2176. PMID: 3560398.

[4] Al-Mallah MH, Hatahet H, Cavalcante JL, Khanal S. Low admission LDL-cholesterol is associated with increased 3-year all-cause mortality in patients with non ST segment elevation myocardial infarction. Cardiol J. 2009;16(3):227-33. PMID: 19437396.

as LDL cholesterol increased, except for patients with LDL cholesterol levels $\geq$ 160 mg/dl."[5]. Wang et al. et al. found that "... hypercholesterolemia was associated with lower in-hospital mortality ... "[6] Reddy et al. reported "... a lipid paradox, with lower LDL-C levels associated with increased risk of in-hospital mortality ... "[7] , [8] . Budzyński et al. investigated the relationship between low-density lipoprotein (LDL-C), acute myocaridal infarction (AMI) and all-cause mortality (ACM) and reported that "... low ... LDL-C levels are risk markers for ACM in patients with AMI ... "[9] A look at scientific history can broaden our view somewhat. In the year 1936, Landé and Sperry shed some new light on our understanding of the still complex relationship between cholesterol and atherosclerosis. In fresh autopsy material in 123 cases of violent death Landé and Sperry compared the lipid content of the aorta with the serum cholesterol content. No relationship was present in any age group between severity of atherosclerosis in man and the blood serum cholesterol content. [10] Besides of the existing and meanwhile increasing evidence to the contrary, lowering of LDL-C cholesterol with standard statin regimens is claimed to be effective against occlusive vascular events. However, more and more, higher mortality in patients with a low cholesterol level are reported. Johannesen et al. published that "... low and high levels of LDL-C were associated with an increased risk of all cause mortality ... "in Denmark. [11] Among several authors [12] Uffe Ravnskov et al. pointed out that "... high cholesterol is not the cause of atherosclerosis ... "[13] At this point we have to ask ourselves, is our general hope justified, that especially atorvastatin protect us against acute myocardial infarction or is atorvastatin just as effective in this respect as a glass of healthy, fresh water?

[5]Cho KH, Jeong MH, Ahn Y, Kim YJ, Chae SC, Hong TJ, Seong IW, Chae JK, Kim CJ, Cho MC, Seung KB, Park SJ; Korea Acute Myocardial Infarction Registry Investigators. Low-density lipoprotein cholesterol level in patients with acute myocardial infarction having percutaneous coronary intervention (the cholesterol paradox). Am J Cardiol. 2010 Oct 15;106(8):1061-8. doi: 10.1016/j.amjcard.2010.06.009. PMID: 20920639.

[6]Wang TY, Newby LK, Chen AY, Mulgund J, Roe MT, Sonel AF, Bhatt DL, DeLong ER, Ohman EM, Gibler WB, Peterson ED. Hypercholesterolemia paradox in relation to mortality in acute coronary syndrome. Clin Cardiol. 2009 Sep;32(9):E22-8. doi: 10.1002/clc.20518. PMID: 19645040; PMCID: PMC6652869.

[7]Reddy VS, Bui QT, Jacobs JR, Begelman SM, Miller DP, French WJ; Investigators of National Registry of Myocardial Infarction (NRMI) 4b–5. Relationship between serum low-density lipoprotein cholesterol and in-hospital mortality following acute myocardial infarction (the lipid paradox). Am J Cardiol. 2015 Mar 1;115(5):557-62. doi: 10.1016/j.amjcard.2014.12.006. Epub 2014 Dec 24. PMID: 25727079.

[8]Amarenco P, Steg PG. The paradox of cholesterol and stroke. Lancet. 2007 Dec 1;370(9602):1803-4. doi: 10.1016/S0140-6736(07)61751-6. PMID: 18061038.

[9]Budzyński J, Tojek K, Wustrau B, Czerniak B, Winiarski P, Korzycka-Wilińska W, Banaszkiewicz Z. The "cholesterol paradox" among inpatients - retrospective analysis of medical documentation. Arch Med Sci Atheroscler Dis. 2018 Mar 27;3:e46-e57. doi: 10.5114/amsad.2018.74736. PMID: 30775589; PMCID: PMC6374572.

[10]Landé, K. E., & Sperry, W. M. (1936). Human atherosclerosis in relation to the cholesterol content of the blood serum. Arch. Pathol., 22, 301-312.

[11]Johannesen CDL, Langsted A, Mortensen MB, Nordestgaard BG. Association between low density lipoprotein and all cause and cause specific mortality in Denmark: prospective cohort study. BMJ. 2020 Dec 8;371:m4266. doi: 10.1136/bmj.m4266. Erratum in: BMJ. 2021 Feb 12;372:n422. PMID: 33293274; PMCID: PMC7722479.

[12]Barukčić, Ilija. (2019). Statins and death due to any cause –all doubts removed?. https://doi.org/10.5281/zenodo.3902771

[13]Ravnskov U, de Lorgeril M, Diamond DM, Hama R, Hamazaki T, Hammarskjöld B, Hynes N, Kendrick M, Langsjoen PH, Mascitelli L, McCully KS, Okuyama H, Rosch PJ, Schersten T, Sultan S, Sundberg R. LDL-C does not cause cardiovascular disease: a comprehensive review of the current literature. Expert Rev Clin Pharmacol. 2018 Oct;11(10):959-970. doi: 10.1080/17512433.2018.1519391. Epub 2018 Oct 11. PMID: 30198808.

2. Material and methods

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

2.1. Material

2.1.1. Studies re-analysed

This study does not claim to be complete, but the results of the study are still usable. In this investigation, the following studies were considered too.

2.1.1.1. Study of Kim et al., 2021 Kim et al. [14] compared the effects of statin therapy, including atrovastatin 40 mg (A40), on major adverse cardiovascular events (MACE) like all-cause death, non-fatal MI undergoing PCI, repeat revascularization, and ischemic stroke in patients with acute myocardial infarction (AMI). "The subjects in the A40 group had the highest proportion of STEMI (23.58%) "

Table 1. The relationship between atorvastatin 40 mg and MACE (Study of Kim et al., 2021).

		MACE		
		YES	NO	
Atorvastatin 40 mg	YES	442	3599	4041
	NO	584	5283	5867
		1026	8882	9908

STATISTICAL ANALYSIS.	
Causal relationship k =	0,01587002
P Value (one sided left tailed) (HGD) =	0,94638902
p (EXCL) =	0,95538958
p (EXCL) approx.= 1-(a/A)) >	0,89062113
p (EXCL) approx.= 1-(a/B)) >	0,56920078
P VALUES.	
P Value (one sided left tailed) (HGD) =	0,94638902
$\tilde{\chi}^2$ (EXCL— A_t) =	48,34545904
$\tilde{\chi}^2$ (EXCL— B_t) =	190,41325536
P Value (EXCL) =	0,04363000
PROPORTIONS.	
(a/A) × 100 =	10,94 %
(b/A) × 100 =	89,06 %
(c/ not A) × 100 =	9,95 %
(d/ not A) × 100 =	90,05 %
(a/B) × 100 =	43,08 %
(c/B) × 100 =	56,92 %
(b/ not B) × 100 =	40,52 %
(d/ not B) × 100 =	59,48 %
(A/N) × 100 =	40,79 %
(not A/N) × 100 =	59,21 %
(B/N) × 100 =	10,36 %
(not B/N) × 100 =	89,64 %
ADDITIONAL STATISTICAL MEASURES.	
RELATIVE RISK (RR).	
RR (necessary condition) =	1,09884557
RR (sufficient condition) =	1,06317274
Relative risk reduction (RRR) =	-9,88 %
OTHER STATISTICAL MEASURES.	
Odds ratio (OR) =	1,11098498
Index of relationship (IOR) =	0,05626297
STUDY DESIGN.	
p(IOU)=	0,48859507
p(IOI)=	0,30429956

[14] Kim K, Bang WD, Han K, Kim B, Lee JM, Chung H. Comparison of the Effects of High-intensity Statin Therapy with Moderate-Intensity Statin and Ezetimibe Combination Therapy on Major Adverse Cardiovascular Events in Patients with Acute Myocardial Infarction: a Nationwide Cohort Study. J Lipid Atheroscler. 2021 Sep;10(3):291-302. doi: 10.12997/jla.2021.10.3.291. Epub 2021 May 25. PMID: 34621700; PMCID: PMC8473958.

Notably, the proportion of subjects with MACE which were **exposed** to Atorvastatin 40 mg is

$$\begin{aligned} p(MACE \backslash Atorvastatin\ 40\ mg) &= \frac{442}{4041} \\ &= 0,109378867 \\ &= 10,93788666\% \end{aligned} \tag{1}$$

and is very high while the follow-up duration (yr) was 2.5±1.1. MACE events occurred about 3-4 % per year, which is to high. Similarly, the proportion of subjects with MACE which were **not exposed** to Atorvastatin 40 mg has been determined as

$$\begin{aligned} p(MACE \backslash \textbf{no}\ \ Atorvastatin\ 40\ mg) &= \frac{584}{4041} \\ &= 0,144518683 \\ &= 14,45186835\% \end{aligned} \tag{2}$$

Nonetheless, the study design of the study of Kim et al. with p(IOI) = 0,304299556 (Barukčić, 2019a) was very unfair . The data of the study of Kim et al. are potentially biased and Kim's data are only of some restricted value.

2.1.1.2. Fisher's exact test Fisher's exact test is a statistical significance test which enable us to calculate the significance of the deviation from a null hypothesis (e.g., P-value) exactly. It is common practice to use Fisher's exact test (Fisher, 1935b) often when the sample is very small but Fisher's exact test is valid for all sample sizes.

$$\begin{aligned} p(X \leq a) &= \sum_{i=0}^{a} \frac{\binom{A}{i}\binom{N-A}{B-i}}{\binom{N}{B}} \\ &= \sum_{i=0}^{442} \frac{\binom{4041}{i}\binom{9908-4041}{1026-i}}{\binom{9908}{1026}} \\ &= 0,946389018 \\ &= \text{P Value (one sided left tailed)} \end{aligned} \tag{3}$$

It is very difficult to re-analysed the data of Kim et al. The causal relationship k is positive and not significant (k = + 0,0158700157; P Value one sided left tailed = 0,9463890181437071). The study design might have had influence on this result.

2.1.1.3. Study of Nilsson et al., 2022 Nilsson et al. investigated the impact of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) on long-term all-cause mortality (ACM) in patients with acute myocardial infarction (AMI) and controls. [15] On statin medication at admission/inclusion (n=731) were 227 cases and 136 controls. Table 2 illustrates these data in more detail.

Table 2. The relationship between statin therapy and AMI (Study of Nilsson et al., 2002).

		AMI		
		YES	NO	
Statin therapy	YES	227	136	363
	NO	504	595	1099
		731	731	1462

STATISTICAL ANALYSIS.	
Causal relationship k =	0,14407520
P Value (one sided left tailed) (HGD) =	0,99999999
p (EXCL) =	0,84473324
p (EXCL) approx.= 1-(a/A)) >	0,37465565
p (EXCL) approx.= 1-(a/B)) >	0,68946648
P VALUES.	
P Value (one sided left tailed) (HGD) =	0,99999999
$\tilde{\chi}^2$ (EXCL— A_t) =	141,95316804
$\tilde{\chi}^2$ (EXCL— B_t) =	70,49110807
P Value (EXCL) =	0,14381325
PROPORTIONS.	
(a/A) × 100 =	62,53 %
(b/A) × 100 =	37,47 %
(c/ not A) × 100 =	45,86 %
(d/ not A) × 100 =	54,14 %
(a/B) × 100 =	31,05 %
(c/B) × 100 =	68,95 %
(b/ not B) × 100 =	18,60 %
(d/ not B) × 100 =	81,40 %
(A/N) × 100 =	24,83 %
(not A/N) × 100 =	75,17 %
(B/N) × 100 =	50,00 %
(not B/N) × 100 =	50,00 %
ADDITIONAL STATISTICAL MEASURES.	
RELATIVE RISK (RR).	
RR (necessary condition) =	1,36359810
RR (sufficient condition) =	1,66911765
Relative risk reduction (RRR) =	-36,36 %
OTHER STATISTICAL MEASURES.	
Odds ratio (OR) =	1,97048611
Index of relationship (IOR) =	0,25068871
STUDY DESIGN.	
p(IOU)=	0,25170999
p(IOI)=	0,25170999

Notably, the proportion of subjects with AMI which were **exposed** to statin therapy at admission to

[15] Nilsson G, Leppert J, Ohrvik J. Enigma of the cholesterol paradox in acute myocardial infarction: lessons from an 8-year follow-up of all-cause mortality in an age-matched and sex-matched case-control study with controls from the patients' recruitment area. BMJ Open. 2022 Jul 27;12(7):e057562. doi: 10.1136/bmjopen-2021-057562. PMID: 35896296; PMCID: PMC9335044.

hospital has been

$$\begin{aligned} p(AMI \backslash Statin\ therapy) &= \frac{227}{363} \\ &= 0,625344353 \\ &= 62,53443526\% \end{aligned} \tag{4}$$

which is to high. There is no evidence that patient did not use statins as prescribed et cetera. Despite proper use of statins, too many patients have suffered myocardial infarction. How is such a fact possible? Statins, if effective against myocardial infarction, must exclude myocardial infarction. Unfortunately, the opposite seems to be the case. The exclusion relationship (see also Barukčić, 2021a) , statin therapy excludes AMI and vice versa is given as **p (EXCL)** $= \left(\frac{136+504+595}{1462}\right) = 0,844733242.$ The approximate exclusion relationship is calculated as **p (EXCL) approx.** $\geq \left(1 - \left(\frac{227}{363}\right)\right) = 0,3746556474$. Considered in all aspects, the result is not statistically significant. In other words, **statin therapy does not exclude AMI** (P Value= 0,143813248) . The study design of the study of Nilsson et al. with p(IOI) = 0,251709986 (Barukčić, 2019a) was very unfair . The data of the study of Nilsson et al. are to some extent potentially biased. Nonetheless, the slightly defective study design affects only the unexposed group (placebo group) and has at the end no systematic effect on the final statistical result. The data presented can be used for our purposes. The conclusion is inevitable.

Therapy with statins is of no help against myocardial infarction and does not prevent myocardial infarction.

2.1.2. Study design and bias

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

2.1.2.1. Index of unfairness (IOU)

Definition 2.1 (Index of unfairness).

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

$$p\left(IOU\left(A,B\right)\right) \equiv Absolute\left(\left(\frac{A+B}{N}\right)-1\right) \tag{5}$$

Under ideal conditions, it is desirable that an appropriate study design is able to assure as much as possible an index of unfairness (see Barukčić, 2019b) of p(IOU) = 0. In point of fact, against the background of lacking enough experience with the use of p(IOU), a p(IOU) up to 0.25 could be of use too. Especially under conditions where **a necessary condition relationship or a sufficient condition relationship** is tested, an index of unfairness is of use to prove whether sample data obtained are biased and to what extent.

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

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

2.1.2.2. Index of independence (IOI)

Definition 2.2 (Index of independence).

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

$$p\left(IOI\left(A,\underline{B}\right)\right) \equiv Absolute\left(\left(\frac{A+\underline{B}}{N}\right)-1\right) \tag{6}$$

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

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

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

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

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

2.1.3. Statistical methods

The probability of the exclusion (Barukčić, 2021c) relationship(see also Barukčić, 2021a) p(EXCL) has been calculated and tested for statistical significance. The chi-square goodness of fit test with one degree of freedom has been used to test whether the sample data published fit a certain theoretical distribution in the population. Additionally, the P Value has been calculated approximately (see also Barukčić, 2019c). The causal relationship k (Barukčić, 2016b, 2020, 2021c) has been calculated to evaluate a possible causal relationship between the events. The hyper-geometric (Fisher, 1922, Gonin, 1936, Huygens and van Schooten, 1657, Pearson, 1899) distribution (HGD) has been used to test the one-sided significance of the causal relationship k. Bringing different studies together for analysing them or doing a meta-analysis is not without problems. Due to several reasons, there is variability in the data of the studies and there will be differences found. Usually, the heterogeneity among the studies is assessed through I^2 statistics [16] , [17] , [18] . Under usual circumstances, an I^2 value of 25%, 50% and 75% are regarded as low, moderate and high heterogeneity[19]. In this publication, the study (design) bias and the heterogeneity among the studies has been controlled by IOI, the index of independence (Barukčić, 2019a) and IOU, the index of unfairness (Barukčić, 2019b). All the data were analysed using MS Excel (Microsoft Corporation, USA).

P values less than 0.05 were considered statistically significant.

2.2. Methods

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

2.2.1. Bernoulli distribution

A single event distribution is more or less a discrete probability distribution of any random variable X which takes a certain (observer independent) single value X_t at a **Bernoulli trial** (Uspensky, 1937,

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

[17] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002 Jun 15;21(11):1539-58. doi: 10.1002/sim.1186. PMID: 12111919.

[18] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003 Sep 6;327(7414):557-60. doi: 10.1136/bmj.327.7414.557. PMID: 12958120; PMCID: PMC192859.

[19] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003 Sep 6;327(7414):557-60. doi: 10.1136/bmj.327.7414.557. PMID: 12958120; PMCID: PMC192859.

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

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

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

In this context, let a random variable A at the *Bernoulli trial* (Uspensky, 1937) (period of time) t, denoted by A_t, indicate a risk factor, a condition, a cause et cetera and occur or exist with the probability p(A_t) at the *Bernoulli trial* (Uspensky, 1937) (period of time) t. Let E(A_t) denote the expectation value of A_t. In general it is

$$p(A_t) \equiv p(a_t) + p(b_t) \tag{7}$$

The expectation value E(A_t) follows as

$$\begin{aligned} E(A_t) &\equiv A_t \times p(A_t) \\ &\equiv A_t \times (p(a_t) + p(b_t)) \\ &\equiv (A_t \times p(a_t)) + (A_t \times p(b_t)) \\ &\equiv E(a_t) + E(b_t) \end{aligned} \tag{8}$$

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

$$\begin{aligned} E(A_t) &\equiv A_t \times p(A_t) \\ &\equiv (+0+1) \times p(A_t) \\ &\equiv p(A_t) \\ &\equiv p(a_t) + p(b_t) \end{aligned} \tag{9}$$

Furthermore, it is

$$p(\underline{A}_t) \equiv p(c_t) + p(d_t) \equiv (1 - p(A_t)) \tag{10}$$

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

$$\begin{aligned} E(\underline{A}_t) &\equiv A_t \times (1 - p(A_t)) \\ &\equiv A_t \times (p(c_t) + p(d_t)) \\ &\equiv (A_t \times p(c_t)) + (A_t \times p(d_t)) \\ &\equiv E(c_t) + E(d_t) \end{aligned} \tag{11}$$

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

$$\begin{aligned} E(\underline{A}_t) &\equiv A_t \times (1 - p(A_t)) \\ &\equiv (+0 + 1) \times (1 - p(A_t)) \\ &\equiv (1 - p(A_t)) \\ &\equiv p(c_t) + p(d_t) \end{aligned} \tag{12}$$

Let a random variable B at the *Bernoulli trial* (Uspensky, 1937) (period of time) t, denoted by B_t, indicate an outcome, a conditioned, an effect et cetera and occur or exist with the probability p(B_t) at the *Bernoulli trial* (Uspensky, 1937) (period of time) t. Let E(B_t) denote the expectation value of B_t. In general it is

$$p(B_t) \equiv p(a_t) + p(c_t) \tag{13}$$

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

$$\begin{aligned} E(B_t) &\equiv B_t \times p(B_t) \\ &\equiv B_t \times (p(a_t) + p(c_t)) \\ &\equiv (B_t \times p(a_t)) + (B_t \times p(c_t)) \\ &\equiv E(a_t) + E(c_t) \end{aligned} \tag{14}$$

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

$$\begin{aligned} E(B_t) &\equiv B_t \times p(B_t) \\ &\equiv (+0 + 1) \times p(B_t) \\ &\equiv p(B_t) \\ &\equiv p(a_t) + p(c_t) \end{aligned} \tag{15}$$

Furthermore, it is

$$p(\underline{B}_t) \equiv p(b_t) + p(d_t) \equiv (1 - p(B_t)) \tag{16}$$

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

$$\begin{aligned} E(\underline{B}_t) &\equiv B_t \times (1 - p(B_t)) \\ &\equiv B_t \times (p(b_t) + p(d_t)) \\ &\equiv (B_t \times p(b_t)) + (B_t \times p(d_t)) \\ &\equiv E(b_t) + E(d_t) \end{aligned} \tag{17}$$

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

$$\begin{aligned} E\left(\underline{B}_t\right) &\equiv B_t \times \left(1 - p\left(B_t\right)\right) \\ &\equiv (+0+1) \times \left(1 - p\left(B_t\right)\right) \\ &\equiv \left(1 - p\left(B_t\right)\right) \\ &\equiv p\left(b_t\right) + p\left(d_t\right) \end{aligned} \tag{18}$$

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

$$\begin{aligned} E\left(a_t\right) &\equiv E\left(A_t \wedge B_t\right) \\ &\equiv \left(A_t \times B_t\right) \times p(A_t \wedge B_t) \\ &\equiv \left(A_t \times B_t\right) \times p(a_t) \end{aligned} \tag{19}$$

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

$$\begin{aligned} E\left(a_t\right) &\equiv E\left(A_t \wedge B_t\right) \\ &\equiv \left(A_t \times B_t\right) \times p(A_t \wedge B_t) \\ &\equiv ((+0+1) \times (+0+1)) \times p(A_t \wedge B_t) \\ &\equiv p(A_t \wedge B_t) \\ &\equiv p\left(a_t\right) \end{aligned} \tag{20}$$

Let $p(b_t)= p(A_t \wedge \neg B_t)$ denote the joint probability distribution of A_t and not B_t at the same Bernoulli trial (period of time) t. In general, it is

$$\begin{aligned} E\left(b_t\right) &\equiv E\left(A_t \wedge \neg B_t\right) \\ &\equiv \left(A_t \times \neg B_t\right) \times p(A_t \wedge \neg B_t) \\ &\equiv \left(A_t \times \neg B_t\right) \times p(b_t) \end{aligned} \tag{21}$$

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

$$\begin{aligned} E\left(b_t\right) &\equiv E\left(A_t \wedge \neg B_t\right) \\ &\equiv \left(A_t \times \neg B_t\right) \times p(A_t \wedge \neg B_t) \\ &\equiv ((+0+1) \times (+0+1)) \times p(A_t \wedge \neg B_t) \\ &\equiv p(A_t \wedge \neg B_t) \\ &\equiv p\left(b_t\right) \end{aligned} \tag{22}$$

Let $p(c_t)= p(\neg A_t \wedge B_t)$ denote the joint probability distribution of not A_t and B_t at the same Bernoulli trial (period of time) t. In general, it is

$$\begin{aligned} E\left(c_t\right) &\equiv E\left(\neg A_t \wedge B_t\right) \\ &\equiv \left(\neg A_t \wedge B_t\right) \times p\left(\neg A_t \wedge B_t\right) \\ &\equiv \left(\neg A_t \wedge B_t\right) \times p(c_t) \end{aligned} \tag{23}$$

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

$$\begin{aligned} E\left(c_{\mathrm{t}}\right) &\equiv E\left(\neg A_{\mathrm{t}} \wedge B_{\mathrm{t}}\right) \\ &\equiv \left(\neg A_{\mathrm{t}} \times B_{\mathrm{t}}\right) \times p(\neg A_{\mathrm{t}} \wedge B_{\mathrm{t}}) \\ &\equiv ((+0+1) \times (+0+1)) \times p\left(\neg A_{\mathrm{t}} \wedge B_{\mathrm{t}}\right) \\ &\equiv p(\neg A_{\mathrm{t}} \wedge B_{\mathrm{t}}) \\ &\equiv p\left(c_{\mathrm{t}}\right) \end{aligned} \tag{24}$$

Let $\mathrm{p(d_t)}$= $\mathrm{p(\neg A_t \wedge \neg B_t)}$ denote the joint probability distribution of not $\mathrm{A_t}$ and not $\mathrm{B_t}$ at the same Bernoulli trial (period of time) t. In general, it is

$$\begin{aligned} E\left(d_{\mathrm{t}}\right) &\equiv E\left(\neg A_{\mathrm{t}} \times \neg B_{\mathrm{t}}\right) \\ &\equiv \left(\neg A_{\mathrm{t}} \times \neg B_{\mathrm{t}}\right) \times p\left(\neg A_{\mathrm{t}} \wedge \neg B_{\mathrm{t}}\right) \\ &\equiv \left(\neg A_{\mathrm{t}} \times \neg B_{\mathrm{t}}\right) \times p(d_{\mathrm{t}}) \end{aligned} \tag{25}$$

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

$$\begin{aligned} E\left(d_{\mathrm{t}}\right) &\equiv E\left(\neg A_{\mathrm{t}} \wedge \neg B_{\mathrm{t}}\right) \\ &\equiv \left(\neg A_{\mathrm{t}} \times \neg B_{\mathrm{t}}\right) \times p(\neg A_{\mathrm{t}} \wedge \neg B_{\mathrm{t}}) \\ &\equiv ((+0+1) \times (+0+1)) \times p\left(\neg A_{\mathrm{t}} \wedge \neg B_{\mathrm{t}}\right) \\ &\equiv p(\neg A_{\mathrm{t}} \wedge \neg B_{\mathrm{t}}) \\ &\equiv p\left(d_{\mathrm{t}}\right) \end{aligned} \tag{26}$$

In general, it is

$$p\left(a_{\mathrm{t}}\right) + p\left(b_{\mathrm{t}}\right) + p\left(c_{\mathrm{t}}\right) + p\left(d_{\mathrm{t}}\right) \equiv +1 \tag{27}$$

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

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

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

In our understanding, it is

$$p\left(B_{\mathrm{t}}\right) + p\left(\Lambda_{\mathrm{t}}\right) \equiv p\left(a_{\mathrm{t}}\right) + p\left(c_{\mathrm{t}}\right) + p\left(\Lambda_{\mathrm{t}}\right) \equiv p\left(a_{\mathrm{t}}\right) + p\left(b_{\mathrm{t}}\right) \equiv p\left(A_{\mathrm{t}}\right) \tag{28}$$

or

$$p\left(c_{\mathrm{t}}\right) + p\left(\Lambda_{\mathrm{t}}\right) \equiv p\left(b_{\mathrm{t}}\right) \tag{29}$$

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

2.2.2. Binomial random variables

The binomial (see Pearson, 1895, p. 351) distribution (see Cramér, 1937) with parameters n and p has been developed by the Swiss mathematician Jakob Bernoulli (1655-1705) in a proof published in his 1713 book Ars Conjectandi (see Bernoulli, 1713) Part 1. In probability theory and statistics, the probability of getting exactly k successes in n independent Bernoulli trials is given by the probability mass function as

$$p\left(X_{\mathrm{t}}=k\right) \equiv \binom{n}{k} \cdot p^{k} \cdot q^{n-k} \tag{30}$$

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

$$p\left(X_{\mathrm{t}} \leq k\right) \equiv 1-p\left(X_{\mathrm{t}}>k\right) \equiv \sum_{t=0}^{k} \binom{n}{t} \cdot p^{t} \cdot q^{n-t} \tag{31}$$

or as

$$p\left(X_{\mathrm{t}}>k\right) \equiv 1-p\left(X_{\mathrm{t}} \leq k\right) \equiv 1-\sum_{t=0}^{k} \binom{n}{t} \cdot p^{t} \cdot q^{n-t} \tag{32}$$

Furthermore, it is

$$p\left(X_{\mathrm{t}}<k\right) \equiv 1-p\left(X_{\mathrm{t}} \geq k\right) \equiv \sum_{t=0}^{k-1} \binom{n}{t} \cdot p^{t} \cdot q^{n-t} \tag{33}$$

or

$$p\left(X_{\mathrm{t}} \geq k\right) \equiv 1-p\left(X_{\mathrm{t}}<k\right) \equiv 1-\sum_{t=0}^{k-1} \binom{n}{t} \cdot p^{t} \cdot q^{n-t} \tag{34}$$

The binomial distribution is the mathematical foundation of a binomial test. The random variable X_t is counting for different things. The discrete geometric (see Feller, 1950, p. 61) distribution describes under certain circumstances the number of Bernoulli trials needed to get one success. The probability that the first occurrence of success requires k independent trials, each with success probability p, is given by the equation

$$p\left(X_{\mathrm{t}}=k\right) \equiv p \cdot q^{k-1} \tag{35}$$

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

$$p\left(X_{\mathrm{t}}=r\right) \equiv \binom{k+r-1}{k-1} p^{k} \cdot q^{r} \tag{36}$$

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

Definition 2.4 (Expectation value and variance of a binomial random variable).

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

$$\sigma\left(X_{\mathrm{t}}\right)^{2} \equiv N \times N \times p\left(X_{\mathrm{t}}\right) \times \left(1 - p\left(X_{\mathrm{t}}\right)\right) \tag{37}$$

Definition 2.5 (Two by two table of Binomial random variables).

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

$$\begin{aligned} A &= N \times E\left(A_{\mathrm{t}}\right) \\ &\equiv N \times \left(A_{\mathrm{t}} \times p\left(A_{\mathrm{t}}\right)\right) \\ &\equiv N \times \left(p\left(A_{\mathrm{t}}\right) + p\left(B_{\mathrm{t}}\right)\right) \\ &\equiv N \times p\left(A_{\mathrm{t}}\right) \end{aligned} \tag{38}$$

and

$$\begin{aligned} B &= N \times E\left(B_{\mathrm{t}}\right) \\ &\equiv N \times \left(B_{\mathrm{t}} \times p\left(B_{\mathrm{t}}\right)\right) \\ &\equiv N \times \left(p\left(A_{\mathrm{t}}\right) + p\left(c_{\mathrm{t}}\right)\right) \\ &\equiv N \times p\left(B_{\mathrm{t}}\right) \end{aligned} \tag{39}$$

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

$$a \equiv N \times \left(E\left(A_{\mathrm{t}}\right)\right) \equiv N \times \left(p\left(A_{\mathrm{t}}\right)\right) \tag{40}$$

and

$$b \equiv N \times \left(E\left(B_{\mathrm{t}}\right)\right) \equiv N \times \left(p\left(B_{\mathrm{t}}\right)\right) \tag{41}$$

and

$$c \equiv N \times \left(E\left(c_{\mathrm{t}}\right)\right) \equiv N \times \left(p\left(c_{\mathrm{t}}\right)\right) \tag{42}$$

and

$$d \equiv N \times \left(E\left(d_{\mathrm{t}}\right)\right) \equiv N \times \left(p\left(d_{\mathrm{t}}\right)\right) \tag{43}$$

and

$$a + b + c + d \equiv A + \underline{A} \equiv B + \underline{B} \equiv N \tag{44}$$

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

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

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

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

(see also Pearson, 1911, p. 159)

2.2.3. Fisher's exact test

In general, the probability mass function of the hyper-geometric distribution (see Fisher, 1922, Gonin, 1936, Huygens and van Schooten, 1657, Pearson, 1899), denoted as p(X = a), is defined as

$$p(X = a) = \frac{\binom{A}{a}\binom{N-A}{B-a}}{\binom{N}{B}} \tag{45}$$

Fisher's exact test is a statistical significance test which is often used in the analysis of contingency tables while applying the hyper-geometric distribution [20]. This statistical methodology opens up the possibility to calculate the significance of the deviation from a null hypothesis (e.g., P Value) exactly. Strangely enough, it is common practice to use Fisher's exact test (Fisher, 1935b) for a sample which is very small. However, it is necessary to point out that Fisher's exact test is valid for all sample sizes without any restriction. Fisher's Exact Test is using the following null and alternative hypotheses:
H0: (null hypothesis)
The two random variables are independent.
H1: (alternative hypothesis)
The two random variables are not independent.

[20] Kim HY. Statistical notes for clinical researchers: Chi-squared test and Fisher's exact test. Restor Dent Endod. 2017 May;42(2):152-155. doi: 10.5395/rde.2017.42.2.152. Epub 2017 Mar 30. PMID: 28503482; PMCID: PMC5426219.

The P Value of an one-sided right tailed Fisher's exact test is calculated as

$$p(X \geq a) = 1 - \sum_{i=0}^{i=a-1} \frac{\binom{A}{i}\binom{N-A}{B-i}}{\binom{N}{B}} \tag{46}$$

The P Value of an one-sided left tailed Fisher's exact test is calculated as

$$p(X \leq a) = \sum_{i=0}^{i=a} \frac{\binom{A}{i}\binom{N-A}{B-i}}{\binom{N}{B}} \tag{47}$$

2.2.4. Bonferroni correction

Sometimes, the more inferences are made on a certain data body (i. e. subgroup analyses), the more likely erroneous inferences might realise. In other words, several independent or dependent statistical tests performed simultaneously on the same data body can induce the so called multiple testing problem. Various statistical techniques have been developed to address this problem. The Bonferroni multiple-comparison correction (see Bonferroni, 1936, Dunn, 1961) is one of the solutions proposed to compensate for the number of inferences being made.

Example

An investigation is testing m = 20 hypotheses with a desired $\alpha = 0.05$. Under these circumstances, the Bonferroni correction proposes to test each individual hypothesis at a single α_{i}

$$\alpha_{\mathrm{i}} = \frac{\alpha}{m} = \frac{0,05}{20} = 0,0025 \tag{48}$$

level where m is the total number hypotheses tested and α is the significance level. By requiring a stricter significance threshold, **an inflation of false positive rates** can be prevented. In the context of further scientific development, there have been several trials to improve the Bonferroni method. One of these attempts is the so called Rom's Method published 1990 by Rom (see Rom, 1990) himself.

2.2.5. Sensitivity and specificity

Definition 2.6 (Sensitivity and specificity)**.**

A (medical) test should measure what is supposed to measure. However, the extent to which a test measures what it is supposed to measure varies and is seldom equal to 100 %. In other words, it is necessary to check once and again the accuracy or the validity of a test, we have to fight it out in detail. In clinical practice, the concept of sensitivity and specificity is commonly used to quantify the diagnostic ability of a (medical) test. Sensitivity and specificity were introduced by the American [21] , [22] , [23] , [24] biostatistician Jacob Yerushalmy (see also Yerushalmy, 1947) in the year 1947. The interior logic of sensitivity and specificity is best illustrated using a conventional two- by-two (2 x 2) table (see table 7).

Table 7. Sensitivity and specificity

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

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

$$Sensitivity\,(A \mid B) \equiv p\,(a \mid B) \equiv \frac{a}{B} \tag{49}$$

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

$$Specificity\,(\underline{A},\underline{B}) \equiv p\,(d \mid \underline{B}) \equiv \frac{d}{\underline{B}} \tag{50}$$

The positive predictive value (PPV) is defined as

$$PPV\,(A,B) \equiv \frac{a}{a+b} \tag{51}$$

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

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

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

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

The negative predictive value (NPV) is defined as

$$NPV\,(A,B) \equiv \frac{d}{c+d} \tag{52}$$

Example.

The importance of sensitivity and specificity in any research should certainly not be underestimated. However, it is essential not to lose sight of the major advantages and limitations [25] of these measures. In the following, in order to avoid misconceptions about sensitivity, specificity et cetera, let us consider a test with a sensitivity of 95 % and a specificity of 95 %. A two-by-two table is used as an illustration (see table 8).

Table 8. Sensitivity and specificity

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

Sensitivity is calculated as

$$Sensitivity\,(A \mid B) \equiv p\,(a \mid B) \equiv 100 \times \frac{a}{B} \equiv \frac{95}{100} \equiv 95\% \tag{53}$$

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

$$SINE\,(A,B) \equiv 100 \times \frac{a+b+d}{N} \equiv \frac{95+5+95}{200} \equiv 97.5\% \tag{54}$$

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

$$Specificity\,(\underline{A} \mid \underline{B}) \equiv p\,(d \mid \underline{B}) \equiv 100 \times \frac{d}{\underline{B}} \equiv \frac{95}{100} \equiv 95\% \tag{55}$$

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

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

$$IMP(A,B) \equiv \frac{a+c+d}{N} \equiv \frac{95+5+95}{200} \equiv 97.5\% \tag{56}$$

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

2.2.6. Odds ratio (OR)

Definition 2.7 (Odds ratio (OR))**.**

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

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

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

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

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

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

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

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

Table 9. The two by two table of random variables

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

$$\begin{aligned} OR(A_t, B_t) &\equiv \left(\frac{a_t}{b_t}\right) / \left(\frac{c_t}{d_t}\right) \\ &\equiv \left(\frac{a_t \times d_t}{b_t \times c_t}\right) \end{aligned} \tag{57}$$

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

Under conditions where (b = 0), the measure of association odds ratio will collapse, because we need to divide by zero, as can be seen at eq. 57. However, according to today's rules of mathematics,

a division by zero is neither allowed nor generally accepted as possible. It does no harm to remind ourselves that in the case $b = 0$ the event A_t is a sufficient condition of B_t. In other words, odds ratio is not able to recognize elementary relationships of objective reality. In fact, it would be a failure not to recognize how dangerous and less valuable odds ratio is.

Under conditions where ($c = 0$) odds ratio collapses too, because we need again to divide by zero, as can be seen at eq. 57. However, and again, today's rules of mathematics don't allow us a division by zero. In point of fact, in the case $c = 0$ it is more than necessary to point out that A_t is a necessary condition of B_t. In other words, odds ratio or the cross-product ratio is not able to recognize elementary relationships of nature like necessary conditions. We can and need to overcome all the epistemological obstacles as backed by odds ratio entirety. Sooner rather than later, we should give up this measure of relationship completely.

2.2.7. Relative risk (RR)

2.2.7.1. Relative risk (RR_{nc})

Definition 2.8 (Relative risk (RR_{nc}))**.**

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

$$\begin{aligned} RR(A_t, B_t)_{nc} &\equiv \frac{\frac{p(a_t)}{p(A_t)}}{\frac{p(c_t)}{p(NotA_t)}} \\ &\equiv \frac{p(a_t) \times p(NotA_t)}{p(c_t) \times p(A_t)} \\ &\equiv \frac{N \times p(a_t) \times N \times p(NotA_t)}{N \times p(c_t) \times N \times p(A_t)} \\ &\equiv \frac{a_t \times (NotA_t)}{c_t \times A_t} \\ &\equiv \frac{EER\,(A_t, B_t)}{CER\,(A_t, B_t)} \end{aligned} \tag{58}$$

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

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

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

2.2.7.2. Relative risk (RR (sc))

Definition 2.9 (Relative risk (RR (sc)))**.**

The relative risk (sc), which provides some evidence of a sufficient condition, is calculated from the point of view of an outcome and is defined as

$$\begin{aligned} RR(A_t,B_t)_{sc} &\equiv \frac{\frac{p(a_t)}{p(B_t)}}{\frac{p(b_t)}{p(NotB_t)}} \\ &\equiv \frac{p(a_t)\times p(NotB_t)}{p(b_t)\times p(B_t)} \\ &\equiv \frac{N\times p(a_t)\times N\times p(NotB_t)}{N\times p(b_t)\times N\times p(B_t)} \\ &\equiv \frac{a_t\times (NotB_t)}{b_t\times B_t} \\ &\equiv \frac{OPR\,(A_t,B_t)}{CPR\,(A_t,B_t)} \end{aligned} \tag{59}$$

2.2.7.3. Relative risk reduction (RRR)

Definition 2.10 (Relative risk reduction (RRR))**.**

$$\begin{aligned} RRR\,(A_t,B_t) &\equiv \frac{CER\,(A_t,B_t)-EER\,(A_t,B_t)}{CER\,(A_t,B_t)} \\ &= 1-RR(A_t,B_t) \end{aligned} \tag{60}$$

2.2.7.4. Vaccine efficacy (VE)

Definition 2.11 (Vaccine efficacy (VE))**.**

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

$$\begin{aligned} VE\,(A_t,B_t) &\equiv 100\times(1-RR\,(A_t,B_t)) \\ &\equiv 100\times\left(\frac{CER\,(A_t,B_t)-EER\,(A_t,B_t)}{CER\,(A_t,B_t)}\right) \end{aligned} \tag{61}$$

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

2.2.7.5. Experimental event rate (EER)

Definition 2.12 (Experimental event rate (EER))**.**

$$EER\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)\equiv\frac{p(a_{\mathrm{t}})}{p(A_{\mathrm{t}})}=\frac{a_{\mathrm{t}}}{a_{\mathrm{t}}+b_{\mathrm{t}}} \tag{62}$$

Definition 2.13 (Control event rate (CER))**.**

$$CER\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)\equiv\frac{p(c_{\mathrm{t}})}{p(\underline{A}_{\mathrm{t}})}=\frac{c_{\mathrm{t}}}{c_{\mathrm{t}}+d_{\mathrm{t}}} \tag{63}$$

2.2.7.6. Absolute risk reduction (ARR)

Definition 2.14 (Absolute risk reducation (ARR))**.**

$$\begin{aligned} ARR\left(A_{\mathrm{t}},B_{\mathrm{t}}\right) &\equiv \frac{p(c_{\mathrm{t}})}{p(\underline{A}_{\mathrm{t}})}-\frac{p(a_{\mathrm{t}})}{p(A_{\mathrm{t}})} \\ &= \frac{c_{\mathrm{t}}}{c_{\mathrm{t}}+d_{\mathrm{t}}}-\frac{a_{\mathrm{t}}}{a_{\mathrm{t}}+b_{\mathrm{t}}} \\ &= CER\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)-EER\left(A_{\mathrm{t}},B_{\mathrm{t}}\right) \end{aligned} \tag{64}$$

2.2.7.7. Absolute risk increase (ARI)

Definition 2.15 (Absolute risk increase (ARI))**.**

$$\begin{aligned} ARI\left(A_{\mathrm{t}},B_{\mathrm{t}}\right) &\equiv \frac{p(a_{\mathrm{t}})}{p(A_{\mathrm{t}})}-\frac{p(c_{\mathrm{t}})}{p(\underline{A}_{\mathrm{t}})} \\ &= EER\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)-CER\left(A_{\mathrm{t}},B_{\mathrm{t}}\right) \end{aligned} \tag{65}$$

2.2.7.8. Number needed to treat (NNT)

Definition 2.16 (Number needed to treat (NNT))**.**

$$NNT\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)\equiv\frac{1}{CER\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)-EER\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)} \tag{66}$$

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

2.2.7.9. Number needed to harm (NNH)

Definition 2.17 (Number needed to harm (NNH))**.**

$$NNH\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)\equiv\frac{1}{EER\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)-CER\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)} \tag{67}$$

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

2.2.7.10. Outcome prevalence rate (OPR)

Definition 2.18 (Outcome prevalence rate (OPR))**.**

$$OPR\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)\equiv\frac{p(a_{\mathrm{t}})}{p(B_{\mathrm{t}})}=\frac{a_{\mathrm{t}}}{a_{\mathrm{t}}+c_{\mathrm{t}}} \tag{68}$$

2.2.7.11. Control prevalence rate (CPR)

Definition 2.19 (Control prevalence rate (CPR))**.**

$$CPR\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)\equiv\frac{p(b_{\mathrm{t}})}{p(\underline{B}_{\mathrm{t}})}=\frac{b_{\mathrm{t}}}{b_{\mathrm{t}}+d_{\mathrm{t}}} \tag{69}$$

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

2.2.7.12. Absolute prevalence reduction (APR)

Definition 2.20 (Absolute prevalence reduction (APR))**.**

$$APR\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)\equiv CPR\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)-OPR\left(A_{\mathrm{t}},B_{\mathrm{t}}\right) \tag{70}$$

2.2.7.13. Absolute prevalence increase (API)

Definition 2.21 (Absolute prevalence increase (API))**.**

$$API\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)\equiv OPR\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)-CPR\left(A_{\mathrm{t}},B_{\mathrm{t}}\right) \tag{71}$$

2.2.7.14. Relative prevalence reduction (RPR)

Definition 2.22 (Relative prevalence reduction (RPR))**.**

$$\begin{aligned} RPR\left(A_{\mathrm{t}},B_{\mathrm{t}}\right) &\equiv \frac{CPR\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)-OPR\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)}{CPR\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)} \\ &= 1-RR(A_{\mathrm{t}},B_{\mathrm{t}})_{\mathrm{sc}} \end{aligned} \tag{72}$$

2.2.7.15. The index NNS

Definition 2.23 (The index NNS)**.**

$$NNS\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)\equiv\frac{1}{CPR\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)-OPR\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)} \tag{73}$$

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

2.2.7.16. The index NNI

Definition 2.24 (The index NNI)**.**

$$NNI\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)\equiv\frac{1}{OPR\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)-CPR\left(A_{\mathrm{t}},B_{\mathrm{t}}\right)} \tag{74}$$

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

2.2.8. Index of relationship (IOR)

Definition 2.25 (Index of relationship (IOR))**.**

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

$$\begin{aligned} IOR(A_t, B_t) &\equiv \left(\frac{p(A_t \wedge B_t)}{p(B_t) \times p(A_t)} \right) - 1 \\ &\equiv \left(\frac{p(a_t)}{p(B_t) \times p(A_t)} \right) - 1 \\ &\equiv \left(\left(\frac{N \times N \times p(a_t)}{N \times p(B_t) \times N \times p(A_t)} \right) - 1 \right) \\ &\equiv \left(\left(\frac{N \times a}{A \times B} \right) - 1 \right) \end{aligned} \tag{75}$$

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

Definition 2.26 (Multi dimensional index of relationship (NIOR))**.**

The multi dimensional index of relationship (NIOR) is defined as

$$\begin{aligned} NIOR(A_t, B_t) &\equiv \left(\frac{N^k \times p({}_1A_t \wedge {}_2A_t \cdots {}_kA_t)}{N \times (p({}_1A_t)) N \times (p({}_2A_t)) \cdots N \times (p({}_kA_t))} \right) - 1 \\ &\equiv \left(\frac{N^{k\text{-}1} \times E({}_1A_t \wedge {}_2A_t \cdots {}_kA_t)}{E({}_1A_t) \times E({}_2A_t) \cdots \times E({}_kA_t)} \right) - 1 \end{aligned} \tag{76}$$

where N is the sample size and $p({}_1A_t \wedge {}_2A_t \cdots {}_kA_t)$ is the joint distribution function.

However, there might exist circumstances where a multi dimensional index of relationship might take the form of the following equation.

$$\begin{aligned} NIOR(A_t, B_t) &\equiv \left(\frac{{}_1N \times {}_2N \times \cdots {}_kN \times p({}_1A_t \wedge {}_2A_t \cdots {}_kA_t)}{({}_1N \times p({}_1A_t)) \times ({}_2N \times p({}_2A_t)) \cdots \times ({}_kN \times p({}_kA_t))} \right) - 1 \\ &\equiv \left(\frac{{}_1N \times {}_2N \times \cdots {}_kN \times p({}_1A_t \wedge {}_2A_t \cdots {}_kA_t)}{E({}_1A_t) \times E({}_2A_t) \cdots \times E({}_kA_t)} \right) - 1 \end{aligned} \tag{77}$$

2.3. Conditions

Even if a condition and a cause are deeply related, there are circumstances where a sharp distinction between a cause and a condition is necessary. However, exactly this has been denied by John Stuart Mill's (1806-1873) regularity view of causality (see Mill, 1843b). What might seem to be a theoretical difficulty for many authors is none for Mill. Mill simply reduced a cause to a condition and claimed that "... the real cause of the phenomenon is the assemblage of all its conditions." (see Mill, 1843a, p. 403)

2.3.1. Exclusion relationship

Definition 2.27 (Exclusion relationship [*EXCL*]).

Mathematically, the exclusion(see also Barukčić, 2021a) relationship [26] (EXCL), denoted by $p(A_t \mid B_t)$ in terms of statistics and probability theory, is defined(see also Barukčić, 1989, p. 68-70) as

$$\begin{aligned} p(A_t \mid B_t) &\equiv p(A_t \uparrow B_t) \\ &\equiv p(b_t) + p(c_t) + p(d_t) \\ &\equiv \frac{N \times (p(b_t) + p(c_t) + p(d_t))}{N} \\ &\equiv \frac{\sum_{t=1}^{N} (\underline{A}_t \vee \underline{B}_t)}{N} \equiv \frac{b+c+d}{N} \\ &\equiv \frac{b+\underline{A}}{N} \\ &\equiv \frac{c+\underline{B}}{N} \\ &\equiv +1 \end{aligned} \tag{78}$$

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

Table 10. A_t excludes B_t and vice versa.

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

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

Example 2.1. *Pfizer Inc. and BioNTech SE* [27] *reported results from a Phase 3 COVID-19 vaccine trial. "A total of ... 43,448 received injections: 21,720 with BNT162b2 and 21,728 with placebo. There were 8 cases of Covid-19 ... among participants assigned to receive BNT162b2 and 162 cases among those assigned to placebo; " (see Polack et al., 2020). The following table (see table 11) provides us with a suitable overview.*

Table 11. BNT162b and COVID-19 (Study Polack et al., 2020).

		COVID-19		
		YES	NO	
BNT162b	YES	8	21712	21720
	NO	162	21566	21728
		170	43278	43448

STATISTICAL ANALYSIS.	
Causal relationship k =	-0,0567641832
p (EXCL) =	0,9998158718
p (EXCL) approx.=	0,9529411765
$\tilde{\chi}^2$ (EXCL— A_t) =	0,0029
$\tilde{\chi}^2$ (EXCL— B_t) =	0,3765
p Value (EXCL) =	0,0001841112
RELATIVE RISK (RR).	
RR (nc) =	0,0494
RR (sc) =	0,0938
Vaccine efficacy (%) =	95,0599
ADDITIONAL MEASURES.	
OR =	0,4965
IOR =	-0,9059
STUDY DESIGN.	
p(IOU)=	0,496179341
p(IOI)=	0,495995213

The exclusion relationship is calculated in detail as follows.

$$\begin{aligned} p\left(Vaccine : BNT162b2 \mid COVID-19(infection)\right) &\equiv p\left(b_t\right)+p\left(c_t\right)+p\left(d_t\right) \\ &\equiv 1-p\left(a_t\right) \\ &\equiv 1-\left(\frac{8}{43538}\right) \\ &\equiv +0,99981625 \end{aligned} \tag{79}$$

[27] Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Moreira ED, Zerbini C, Bailey R, Swanson KA, Roychoudhury S, Koury K, Li P, Kalina WV, Cooper D, Frenck RW Jr, Hammitt LL, Türeci Ö, Nell H, Schaefer A, Ünal S, Tresnan DB, Mather S, Dormitzer PR, Şahin U, Jansen KU, Gruber WC; C4591001 Clinical Trial Group. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020 Dec 31;383(27):2603-2615. doi: 10.1056/NEJMoa2034577. Epub 2020 Dec 10. PMID: 33301246; PMCID: PMC7745181.

with a P Value = 0,000184.

2.3.1.1. Fisher's exact test Fisher's exact test is a statistical significance test which enable us to calculate the significance of the deviation from a null hypothesis (e.g., P-value) exactly. It is common practice to use Fisher's exact test (Fisher, 1935b) often when the sample is very small but Fisher's exact test is valid for all sample sizes.

$$\begin{aligned} p(X \leq a) &= \sum_{i=0}^{a} \frac{\binom{A}{i}\binom{N-A}{B-i}}{\binom{N}{B}} \\ &= \sum_{i=0}^{8} \frac{\binom{21720}{i}\binom{43448-21720}{170-i}}{\binom{43448}{170}} \\ &= \frac{6.7686358877995}{100\,000\,000\,000\,000\,000\,000} \\ &= 6.7686358877995e-20 \\ &= \text{P Value (one sided left tailed)} \end{aligned} \tag{80}$$

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

$$\begin{aligned} p\left(A_t \mid B_t\right) &\equiv p\left(\underline{A}_t \cup \underline{B}_t\right) \\ &\equiv 1 - p\left(A_t \cap B_t\right) \\ &\equiv 1 - \int_{-\infty}^{A_t}\int_{-\infty}^{B_t} f\left(A_t, B_t\right)\, dA_t\, dB_t \\ &\equiv +1 \end{aligned} \tag{81}$$

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

2.3.2. Observational study and exclusion relationship

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

$$p\left(A_t \mid B_t\right) \equiv p\left(A_t \uparrow B_t\right) \geq 1 - \frac{p\left(a_t\right)}{p\left(B_t\right)} \tag{82}$$

2.3.3. Experimental study and exclusion relationship

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

$$p\left(A_{\mathrm{t}} \mid B_{\mathrm{t}}\right) \equiv p\left(A_{\mathrm{t}} \uparrow B_{\mathrm{t}}\right) \geq 1-\frac{p\left(a_{\mathrm{t}}\right)}{p\left(A_{\mathrm{t}}\right)} \tag{83}$$

2.3.4. The goodness of fit test of an exclusion relationship

Definition 2.28 (The $\tilde{\chi}^2$ goodness of fit test of an exclusion relationship).

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

$$\begin{aligned} \tilde{\chi}^2{}_{\text{Calculated}}\left(\left(A_{\mathrm{t}} \mid B_{\mathrm{t}}\right) \mid A\right) &\equiv \frac{(b-(a+b))^2}{A}+ \\ &\quad \frac{((c+d)-\underline{A})^2}{\underline{A}} \\ &\equiv \frac{a^2}{A}+0 \\ &\equiv \frac{a^2}{A} \end{aligned} \tag{84}$$

or equally as

$$\begin{aligned} \tilde{\chi}^2{}_{\text{Calculated}}\left(\left(A_{\mathrm{t}} \mid B_{\mathrm{t}}\right) \mid B\right) &\equiv \frac{(c-(a+c))^2}{B}+ \\ &\quad \frac{((b+d)-\underline{B})^2}{\underline{B}} \\ &\equiv \frac{a^2}{B}+0 \\ &\equiv \frac{a^2}{B} \end{aligned} \tag{85}$$

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 $\mathrm{p}(\mathrm{A_t} \mid \mathrm{B_t})$, in which case the null hypothesis has to be accepted. Yate's (Yates, 1934) continuity correction was not used under these circumstances.

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

Definition 2.29 (The left-tailed p Value of an exclusion relationship).

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

$$\begin{aligned} pValue_{\mathrm{lt}}\left(A_{\mathrm{t}} \mid B_{\mathrm{t}}\right) &\equiv 1 - e^{-(1-p(A_{\mathrm{t}}|B_{\mathrm{t}}))} \\ &\equiv 1 - e^{-(a/N)} \end{aligned} \tag{86}$$

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

2.4. Causation

2.4.1. Causation in general

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

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

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

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

as a fundamental law of nature and rightly too. Meanwhile, Heisenberg's uncertainty principle is refuted (see Barukčić, 2011a, 2014, 2016a) for several times but still not exterminated completely out of physics and out of science as such.

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

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

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

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

In 1965, Sir Austin Bradford Hill (Hill, 1965) published nine criteria (the '*Bradford Hill Criteria* ') in order to determine whether observed epidemiological associations are causal. Somewhat worrying, is at least the fact that, Hill's "... fourth characteristic is *the temporal relationship of the association* " and so-to-speak just a reformulation of the '*post hoc ergo propter hoc'(Barukčić, 1989, Woods and Walton, 1977)* logical fallacy through the back-door and much more then this. It is questionable whether association as such can be treated as being identical with causation. Unfortunately, due to several reasons, it seems therefore rather problematic to rely on Bradford Hill Criteria carelessly.

Meanwhile, several other and competing mathematical or statistical approaches for causal inference have been discussed by various modern authors (Barukčić, 1989, 1997, 2005, 2016b, 2017a,b, Bohr, 1937, Chisholm, 1946, Dempster, 1990, Espejo, 2007, Goodman, 1947, Granger, 1969, Hessen, Johannes, 1928, Hesslow, 1976, 1981, Korch, Helmut, 1965, Lewis, David Kellogg, 1973, 1974, Pearl, 2000, Schlick, Friedrich Albert Moritz, 1931, Spohn, 1983, Suppes, 1970, Todd, 1968, Zesar, 2013) or even established (Barukčić, 1989, 1997, 2005, 2016b, 2017a,b). Nevertheless, the question is still

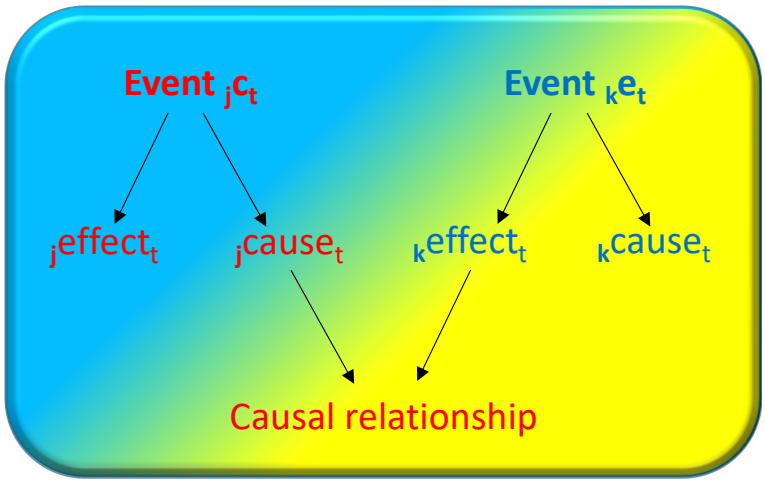
not answered, is it at all possible to establish a cause effect relationship between two factors while applying only certain statistical (Sober, 2001) methods?

2.4.2. Cause and effect

Besides all, there are several further aspects of causation for which our attention so far has not been adequately fixed in this context. In the causal relationship, cause and effect are united, a cause is an effect and an effect is a cause.

> "Thus, in the causal relation, cause and effect are inseparable; a cause which had no effect would not be a cause, just as an effect which had no cause would no longer be an effect. "
>
> (see Hegel, Georg Wilhelm Friedrich, 1991, p. 151)

The unity of cause and effect is a unity of two which are not the same. Cause and effect as inseparable in the causal relation are at the same time mutually related as sheer others; each of both as united in its own self to the other of itself is able to passes over into its own other and vice versa. Yet, to approach from a different point of view, a cause and an effect are separated in the same relation too, a cause is not an effect and an effect is not a cause, both are different in the same relation.



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"Therefore, though the cause has an effect and is at the same time itself effect, and the effect not only has a cause but is also itself cause, yet the effect which the cause has, and the effect which it is, are different, as are also the cause which the effect has, and the cause which it is." (see Hegel, Georg Wilhelm Friedrich, 1991, p. 565/566)

2.4.2.1. What is a cause, what is an effect? An important fact to which we must pay attention here is that in a causal relation, under certain circumstances, an individual cause and an individual effect are related to each other in their own particular way. An effect which vanishes in its own cause in the same respect equally becomes again in it and vice versa. A cause which is merely extinguished in its own effect becomes again in the same. In fact, each of these determinations presupposes in its own other its own self and constitutes the intimate tie between an individual cause and its own individual

effect. Thus far, under conditions of a **positive** causal relationship k, an event U_t which is for sure a cause of another event W_t is at the same time t a necessary and sufficient condition of an event W_t. Table 12 may illustrate this relationship. A matter of great theoretical importance is the fundamental

Table 12. What is the cause, what is the effect?

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

relationship between a cause and a condition. Are both, cause and condition, at the end identical? As of now, following Mill (see Mill, 1843a, p. 403), Verworn (see Verworn, 1912), Mackie and others, we can give a clear 'Yes'in reply to this question: "... cause is ... a condition which is itself ... *sufficient* ... " (see Mackie, 1965, p. 245). However, this issue is not as simple as it sounds, according to Mackie. Thus far, it is essential to eliminate some errors. Indeed, there are circumstances where a cause and a condition are identical, a cause and a condition are equivalent. However, as outlined in this publication, both, a cause and a condition, are different too and a cause and a condition are not identical either.

> "Jede Ursache ist nothwendig auch eine Bedingung eines Ereignisses;
> aber nicht jede Bedingung ist Ursache zu nennen. "
>
> (see Bar, Carl Ludwig von, 1871, p. 4)

The crux of the matter is that not every condition is a cause too, in German: "... nicht jede Bedingung ist Ursache ... "(see Bar, Carl Ludwig von, 1871, p. 4). However, and in contrast to a condition, every cause as such is indeed a condition too, in German: "Jede Ursache ist ... auch eine Bedingung ... "(see Bar, Carl Ludwig von, 1871, p. 4). In general, a cause U_t is a necessary condition of an effect W_t. In other words, **without** a cause U_t **no** effect W_t. One consequence of the necessary condition relationship between cause and effect is that "... an effect which had no cause would no longer be an effect. " (see Hegel, Georg Wilhelm Friedrich, 1991, p. 151). However, a cause U_t being a necessary condition of an effect W_t is equivalent to an effect W_t being a sufficient condition of the same cause U_t and vice versa too. In our everyday words,

without

U_t

no

W_t

is equivalent with

if

W_t

then

U_t

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

$$(U_t \vee \underline{W}_t) \equiv (\underline{W}_t \vee U_t) \equiv ((U_t \vee \underline{W}_t) \wedge (\underline{W}_t \vee U_t)) \equiv +1 \tag{87}$$

		Effect W_t		
		TRUE	FALSE	
Cause	TRUE	a_t	b_t	U_t
U_t	FALSE	$c_t = 0$	d_t	$\underline{U}_t$
		W_t	$\underline{W}_t$	+1

Table 13. Without U_t no W_t

		Cause U_t		
		TRUE	FALSE	
Effect	TRUE	a_t	$c_t = 0$	W_t
W_t	FALSE	b_t	d_t	$\underline{W}_t$
		U_t	$\underline{U}_t$	+1

Table 14. If W_t then U_t

The other side of the causal relation at the same (period of) time / Bernoulli trial t is the fact that a cause U_t is equally a sufficient condition of an effect W_t too or shortly **if** cause U_t **then** effect W_t. One straightforward consequence of this fundamental relationship between a cause and an effect is that "... a cause which had no effect would not be a cause ... " (see Hegel, Georg Wilhelm Friedrich, 1991, p. 151). But even this is not without difficulties, because a cause U_t being a sufficient condition of an effect W_t is equivalent to effect W_t being a necessary condition of the same cause U_t. In different words,

if

U_t

then

W_t

is equivalent with

without

W_t

no

U_t.

		Effect W_t		
		TRUE	FALSE	
Cause	TRUE	a_t	$b_t = 0$	U_t
U_t	FALSE	c_t	d_t	$\underline{U}_t$
		W_t	$\underline{W}_t$	+1

Table 15. If U_t then W_t

		Cause U_t		
		TRUE	FALSE	
Effect	TRUE	a_t	c_t	W_t
W_t	FALSE	$b_t = 0$	d_t	$\underline{W}_t$
		U_t	$\underline{U}_t$	+1

Table 16. Without W_t no U_t

To bring it to the point, necessary and sufficient conditions are at the end converses (see Gomes, Gilberto, 2009) of each other and far more than this. In fact, there is a kind of reciprocity or mirroring between cause and effect. Necessary and sufficient conditions are relationships used to describe the relationship between two events at the same Bernoulli trial t. In more detail, if U_t then W_t is equivalent with W_t is necessary for U_t, because the truth of U_t guarantees the truth of W_t. In general, it is

$$(\underline{U}_t \vee W_t) \equiv (W_t \vee \underline{U}_t) \equiv ((\underline{U}_t \vee W_t) \wedge (W_t \vee \underline{U}_t)) \equiv +1 \tag{88}$$

In other words, it is impossible to have U_t without W_t (Bloch, 2011). Similarly, U_t is sufficient for W_t, because U_t being true always implies that W_t is true, but U_t not being true does not always imply that W_t is not true. And we should use this relationships to make our point. In general, **without** gaseous oxygen (U_t), there is **no** burning wax candle (W_t); hence the relationship **if** burning wax candle (W_t) **then** gaseous oxygen (U_t) is equally true and given. This everyday knowledge is known and secured since centuries and might be illustrated as follows.

		Wax candle B_t		
		burning	not burning	
Gaseous	present	a_t	b_t	A_t
oxygen_t	not present	$c_t = 0$	d_t	$\underline{A}_t$
		B_t	$\underline{B}_t$	+1

Table 17. Without A_t no B_t

		Gaseous oxygen A_t		
		present	not present	
Wax candle	burning	a_t	$c_t = 0$	B_t
	not burning	b_t	d_t	$\underline{B}_t$
		A_t	$\underline{A}_t$	+1

Table 18. If B_t then A_t

Nonetheless, and independently of this secured everyday knowledge, **a burning wax candle is a sufficient condition of gaseous oxygen but not the cause of gaseous oxygen**.

Given all the circumstances, it is at least this simple **counter-example** which provides us with a convincing evidence that **a sufficient condition alone is not enough to describe a cause completely**. In general, a cause as such cannot be reduced to a simple sufficient condition.

In contrast to this obvious fact, other authors prefer another approach to the definition of a cause. "So that, more explicitly, if a given particular event is regarded as having been sufficient to the occurrence of another, it is said to have been its cause; if regarded as having been necessary to the occurrence of another, it is said to have been a condition of it; ..." (see Ducasse, 1926, p. 58). Therefore, in order

to be a cause of oxygen, additional evidence is necessary that a burning wax candle is a necessary condition of gaseous oxygen too. However, even if the relationship **without** gaseous oxygen **no** burning wax candle is given, this relationship is not given vice versa. The relationship **without** burning wax candle **no** gaseous oxygen is not given. Like other fundamental concepts, the concepts of cause and effect can be associated with difficulties too. Under certain conditions, the causal relationship between U_t and W_t, when correctly defined and recognised, is closely allied with the requirement that a certain study or that at least other, different studies provided evidence of a necessary condition between U_t and W_t and of a sufficient condition between U_t and W_t and if possible of **a necessary and sufficient condition** between U_t and W_t too.

Mathematically, a necessary and sufficient condition between U_t and W_t is defined as

$$(U_t \vee \underline{W}_t) \wedge (\underline{U}_t \vee W_t) \equiv +1 \tag{89}$$

However, I think it necessary to make a clear distinction between a necessary and sufficient condition and the converse relationship (Eq. 87) above.

$$((U_t \vee \underline{W}_t) \wedge (\underline{W}_t \vee U_t)) \neq (U_t \vee \underline{W}_t) \wedge (\underline{U}_t \vee W_t) \tag{90}$$

2.4.2.2. The direction of causation In general, a cause is related to its own effect in its own way and vice versa (see Mackie, 1966, p. 160) too. The effect (see Black, 1956) of this cause is itself related to its own cause in some way in which the cause is not related to its own effect (see Dummett and Flew, 1954). This can be considered as one of the reasons why the relation between cause and effect is taken to be asymmetrical.

2.4.2.3. The priority of cause to effect Contemporary discussions of causation are greatly influenced by the causal relation that 'an effect W_t is causally dependent upon a cause U_t'. However, under certain conditions (mono-causality), to say that 'an effect W_t is causally dependent upon a cause U_t'is to say that 'if a cause U_t had not occurred, then an effect W_t would not have occurred too.' (see Lewis, David Kellogg, 1973, 1974). However, what came first, the hen or the egg, the cause or the effect?

2.4.3. Definition causal relationship k

Definition 2.30 (Causal relationship k).

Nonetheless, mathematically, the causal(Barukčić, 2011a,b, 2012) relationship (Barukčić, 1989, 1997, 2005, 2016b, 2017a,b, 2021c) between a cause U_t (German: Ursache) and an effect W_t (German: Wirkung), denoted by k(U_t, W_t), is defined *at each single(Thompson, 2006) Bernoulli trial t* in terms of statistics and probability theory [28] , [29] , [30] as

$$\begin{aligned} k(U_t, W_t) &\equiv \frac{\sigma(U_t, W_t)}{\sigma(U_t) \times \sigma(W_t)} \\ &\equiv \frac{p(U_t \wedge W_t) - p(U_t) \times p(W_t)}{\sqrt[2]{(p(U_t) \times (1 - p(U_t))) \times (p(W_t) \times (1 - p(W_t)))}} \end{aligned} \tag{91}$$

where σ (U_t , W_t) denotes the co-variance between a cause U_t and an effect W_t *at every single Bernoulli trial t*, σ (U_t) denotes the standard deviation of a cause U_t at the same single Bernoulli trial t, σ (W_t) denotes the standard deviation of an effect W_t at same single Bernoulli trial t. Table 19 illustrates the theoretically possible relationships between a cause and an effect.

Table 19. Sample space and the causal relationship k

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

However, even if one thinks to recognise the trace of Bravais (Bravais, 1846) (1811-1863) - Pearson's (1857-1936) "*product-moment coefficient of correlation*"(Galton, 1877, Pearson, 1896) inside the causal relationship k (Barukčić, 1989, 1997, 2005, 2016b, 2017a,b) 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

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

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

[30] Ilija Barukčić. The causal relationship k. MATEC Web Conf., 336 (2021) 09032 DOI: https://doi.org/10.1051/matecconf/202133609032

coefficient(Pearson, 1904b), is defined at every single Bernoulli trial t. This might be a very *small* difference. However, even a small difference might determine a difference. However, in this context and in any case, this small difference *makes*(Barukčić, 2018) the difference.

2.4.4. Statistical methods

The probability of the exclusion (Barukčić, 2021c) relationship(see also Barukčić, 2021a) p(EXCL) has been calculated and tested for statistical significance. The chi-square goodness of fit test with one degree of freedom has been used to test whether the sample data published fit a certain theoretical distribution in the population. Additionally, the P Value has been calculated approximately (see also Barukčić, 2019c). The causal relationship k (Barukčić, 2016b, 2020, 2021c) has been calculated to evaluate a possible causal relationship between the events. The hyper-geometric (Fisher, 1922, Gonin, 1936, Huygens and van Schooten, 1657, Pearson, 1899) distribution (HGD) has been used to test the one-sided significance of the causal relationship k. Bringing different studies together for analysing them or doing a meta-analysis is not without problems. Due to several reasons, there is variability in the data of the studies and there will be differences found. Usually, the heterogeneity among the studies is assessed through I^2 statistics [31] , [32] , [33] . Under usual circumstances, an I^2 value of 25%, 50% and 75% are regarded as low, moderate and high heterogeneity[34]. In this publication, the study (design) bias and the heterogeneity among the studies has been controlled by IOI, the index of independence (Barukčić, 2019a) and IOU, the index of unfairness (Barukčić, 2019b). All the data were analysed using MS Excel (Microsoft Corporation, USA).

P values less than 0.05 were considered statistically significant.

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

[32] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002 Jun 15;21(11):1539-58. doi: 10.1002/sim.1186. PMID: 12111919.

[33] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003 Sep 6;327(7414):557-60. doi: 10.1136/bmj.327.7414.557. PMID: 12958120; PMCID: PMC192859.

[34] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003 Sep 6;327(7414):557-60. doi: 10.1136/bmj.327.7414.557. PMID: 12958120; PMCID: PMC192859.

3. Results

3.1. Simvastatin

Drug therapy for hypercholesterolaemia is still controversial. The randomised trial of cholesterol lowering in 4444 patients with coronary heart disease (the Scandinavian Simvastatin Survival Study (4S)) (see Pedersen and 4S, 1994) provided the following data. The median follow-up period was about 5.4 years.

Table 20. The relationship between simvastatin and coronary events (Study of 4 S Study Group, 1994).

		Coronary events		
		YES	NO	
Simvastatin	YES	431	1790	2221
	NO	622	1601	2223
		1053	3391	4444

STATISTICAL ANALYSIS.	
Causal relationship k =	-0,10082691
P Value (one sided left tailed) (HGD) =	0,00000000
p (EXCL) =	0,90301530
p (EXCL) approx.= 1-(a/A)) >	0,80594327
p (EXCL) approx.= 1-(a/B)) >	0,59069326
P VALUES.	
P Value (one sided left tailed) (HGD) =	0,00000000
$\tilde{\chi}^2$ (EXCL— A_t) =	83,63845115
$\tilde{\chi}^2$ (EXCL— B_t) =	176,41120608
P Value (EXCL) =	0,09243011
PROPORTIONS.	
(a/A) × 100 =	19,41 %
(b/A) × 100 =	80,59 %
(c/ not A) × 100 =	27,98 %
(d/ not A) × 100 =	72,02 %
(a/B) × 100 =	40,93 %
(c/B) × 100 =	59,07 %
(b/ not B) × 100 =	52,79 %
(d/ not B) × 100 =	47,21 %
(A/N) × 100 =	49,98 %
(not A/N) × 100 =	50,02 %
(B/N) × 100 =	23,69 %
(not B/N) × 100 =	76,31 %
ADDITIONAL STATISTICAL MEASURES.	
RELATIVE RISK (RR).	
RR (necessary condition) =	0,69355002
RR (sufficient condition) =	0,77539618
Relative risk reduction (RRR) =	30,64 %
OTHER STATISTICAL MEASURES.	
Odds ratio (OR) =	0,61976235
Index of relationship (IOR) =	-0,18101794
STUDY DESIGN.	
p(IOU)=	0,26327633
p(IOI)=	0,26282628

3.1.0.1. Fisher's one sided left tailed exact test The hyper-geometric distribution (HGD) describes the probability of x successes in N **draws without replacement** while the same distribution is valid for all sample sizes. In contrast to the hyper-geometric distribution, the binomial distribution describes the probability of x successes in N **draws with replacement**. The one sided left tailed P Value is used when the alternative to independence is that there is a **negative relationship** between the variables investigated. Fisher's exact test (Fisher, 1935b) is a statistical significance test which is based on the hyper-geometric distribution and enable us to calculate the significance of the deviation from a null hypothesis (e.g., P Value) exactly. The left tailed P Value (no replacement, hyper-geometric distribution) (see also Fisher's exact test (see also Barnard, 1945, Boschloo, 1970, Fisher, 1935b)) is calculated as follows:

$$\begin{aligned} p(X \leq a) &= \sum_{i=0}^{a} \frac{\binom{A}{i}\binom{N-A}{B-i}}{\binom{N}{B}} \\ &= \sum_{i=0}^{431} \frac{\binom{2221}{i}\binom{4444-2221}{1053-i}}{\binom{4444}{1053}} \\ &= 0,0000000000 \\ &= \text{P Value (one sided left tailed)} \end{aligned} \tag{92}$$

Nonetheless, the data of the study which have been published by 4 S Study Group are contradictory. The study design (see also Barukčić, 2019a) of the study proofed to be p(IOI) = 0,262826283 and is very unfair. The data can only be viewed with some restrictions. Further abnormalities in the data presented are apparent. The proportion (a/A) = 19,41 % is implausibly high. The proportion (c / not A) = 27,98 % and is more or less inconsistent with known facts. Based on the data of the study of 4 S Study Group we have to accept that in the total population in about (b/ not B) $\times$ 100 = 52,79 % subjects are exposed to Simvastatin or in other words are Simvastatin positive. This does not seem to be in line with reality. In total, 1053 events were observed. In the group not exposed to Simvastatin 622 events were observed. The relative risk reduction is RRR = 30,64 % and indicates some benefit for patient treated with Simvastatin . However, this seems to be true only superficially. If Simvastatin effectively precluded coronary events, then there should not have been a single event in the Simvastatin group. However, contrary to all expectations 431 occured in the Simvastatin group. The exclusion relationship has been calculated as p(EXCL) = 0,90301530 and is not statistically significant (P Value = 0,092430107). All in all, the results based on these data demand us all more or less to consider in greater detail whether Simvastatin is of any value in the prevention of coronary events . There is also the question of whether Simvastatin is in some sense virostatic.

3.2. *Pravastatin*

A very great hope is that lowering the blood cholesterol level may reduce the risk of myocardial infarction (MI) and of other coronary events too. Shepherd et al. [35] conducted a placebo controlled, double-blind study to determine whether the administration of pravastatin (see Shepherd et al., 1995) has the potential to reduce coronary events.

Table 21. The relationship between pravastatin and non fatal MI (Study of Shepherd et al., 1995).

		Non fatal MI		
		YES	NO	
Pravastatin	YES	143	3159	3302
	NO	204	3089	3293
		347	6248	6595

STATISTICAL ANALYSIS.	
Causal relationship k =	-0,04174970
P Value (one sided left tailed) (HGD) =	0,00041521
p (EXCL) =	0,97831691
p (EXCL) approx.= 1-(a/A)) >	0,95669291
p (EXCL) approx.= 1-(a/B)) >	0,58789625
P VALUES.	
P Value (one sided left tailed) (HGD) =	0,00041521
$\tilde{\chi}^2$ (EXCL— A_t) =	6,19291339
$\tilde{\chi}^2$ (EXCL— B_t) =	58,93083573
P Value (EXCL) =	0,02144970
PROPORTIONS.	
(a/A) × 100 =	4,33 %
(b/A) × 100 =	95,67 %
(c/ not A) × 100 =	6,19 %
(d/ not A) × 100 =	93,81 %
(a/B) × 100 =	41,21 %
(c/B) × 100 =	58,79 %
(b/ not B) × 100 =	50,56 %
(d/ not B) × 100 =	49,44 %
(A/N) × 100 =	50,07 %
(not A/N) × 100 =	49,93 %
(B/N) × 100 =	5,26 %
(not B/N) × 100 =	94,74 %
ADDITIONAL STATISTICAL MEASURES.	
RELATIVE RISK (RR).	
RR (necessary condition) =	0,69906979
RR (sufficient condition) =	0,81507572
Relative risk reduction (RRR) =	30,09 %
OTHER STATISTICAL MEASURES.	
Odds ratio (OR) =	0,68544743
Index of relationship (IOR) =	-0,17691575
STUDY DESIGN.	
p(IOU)=	0,44670205
p(IOI)=	0,44806672

[35] Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med. 1995 Nov 16;333(20):1301-7. doi: 10.1056/NEJM199511163332001. PMID: 7566020.

3.2.0.1. Fisher's one sided left tailed exact test The hyper-geometric distribution (HGD) describes the probability of x successes in N **draws without replacement** while the same distribution is valid for all sample sizes. In contrast to the hyper-geometric distribution, the binomial distribution describes the probability of x successes in N **draws with replacement** . The one sided left tailed P Value is used when the alternative to independence is that there is a **negative relationship** between the variables investigated. Fisher's exact test (Fisher, 1935b) is a statistical significance test which is based on the hyper-geometric distribution and enable us to calculate the significance of the deviation from a null hypothesis (e.g., P Value) exactly. The left tailed P Value (no replacement, hyper-geometric distribution) (see also Fisher's exact test (see also Barnard, 1945, Boschloo, 1970, Fisher, 1935b)) is calculated as follows:

$$\begin{aligned} p(X \leq a) &= \sum_{i=0}^{a} \frac{\binom{A}{i}\binom{N-A}{B-i}}{\binom{N}{B}} \\ &= \sum_{i=0}^{143} \frac{\binom{3302}{i}\binom{6595-3302}{347-i}}{\binom{6595}{347}} \\ &= 0,0004152078 \\ &= \text{P Value (one sided left tailed)} \end{aligned} \tag{93}$$

Nonetheless, the data of the study which have been published by Shepherd et al. are contradictory. The study design (see also Barukčić, 2019a) of the study proofed to be p(IOI) = 0,448066717 and is very unfair. The data can only be viewed with some restrictions. Further abnormalities in the data presented are apparent. The proportion (a/A) = 4,33 % is implausibly high. The proportion (c / not A) = 6,19 % and is more or less inconsistent with known facts. Based on the data of the study of Shepherd et al. we have to accept that in the total population in about (b/ not B) $\times$ 100 = 50,56 % subjects are exposed to pravastatin or in other words are pravastatin positive. This does not seem to be in line with reality. In total, 347 events were observed. In the group not exposed to pravastatin 204 events were observed. The relative risk reduction is RRR = 30,09 % and indicates some benefit for patient treated with pravastatin . However, this seems to be true only superficially. If pravastatin effectively precluded coronary events, then there should not have been a single event in the pravastatin group. However, contrary to all expectations 143 occured in the pravastatin group. The exclusion relationship has been calculated as p(EXCL) = 0,97831691 and is not statistically significant (P Value = 0,021449705; see also the chi-square values). All in all, the results based on these data demand us all more or less to cosider in greater detail whether pravastatin is of any value in the prevention of non fatal MI .

3.3. Atorvastatin

The group around Terje R Pedersen et al. [36] conducted a prospective, randomized, open-label, blinded study (IDEAL). Patients were randomly assigned and received either a high dose of atorvastatin (80 mg/d; n = 4439), or an usual-dose simvastatin (20 mg/d; n = 4449). Several types of events were documented. Table 22 is providing us with the data and the necessary analysis.

Table 22. The relationship between atorvastatin 80 mg and any coronary event (Study of Pedersen et al. , 2005).

		Any coronary event		
		YES	NO	
Atorvastatin 80 mg	YES	1176	3263	4439
	NO	1370	3079	4449
		2546	6342	8888

STATISTICAL ANALYSIS.	
Causal relationship k =	-0,04756628
P Value (one sided left tailed) (HGD) =	0,00000405
p (EXCL) =	0,86768677
p (EXCL) approx.= 1-(a/A)) >	0,73507547
p (EXCL) approx.= 1-(a/B)) >	0,53809898
P VALUES.	
P Value (one sided left tailed) (HGD) =	0,00000405
$\tilde{\chi}^2$ (EXCL— A_t) =	311,55125028
$\tilde{\chi}^2$ (EXCL— B_t) =	543,19560094
P Value (EXCL) =	0,12393346
PROPORTIONS.	
(a/A) × 100 =	26,49 %
(b/A) × 100 =	73,51 %
(c/ not A) × 100 =	30,79 %
(d/ not A) × 100 =	69,21 %
(a/B) × 100 =	46,19 %
(c/B) × 100 =	53,81 %
(b/ not B) × 100 =	51,45 %
(d/ not B) × 100 =	48,55 %
(A/N) × 100 =	49,94 %
(not A/N) × 100 =	50,06 %
(B/N) × 100 =	28,65 %
(not B/N) × 100 =	71,35 %
ADDITIONAL STATISTICAL MEASURES.	
RELATIVE RISK (RR).	
RR (necessary condition) =	0,86032792
RR (sufficient condition) =	0,89775552
Relative risk reduction (RRR) =	13,97 %
OTHER STATISTICAL MEASURES.	
Odds ratio (OR) =	0,80998946
Index of relationship (IOR) =	-0,07515741
STUDY DESIGN.	
p(IOU)=	0,21410891
p(IOI)=	0,21298380

[36] Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I, Larsen ML, Bendiksen FS, Lindahl C, Szarek M, Tsai J; Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) Study Group. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. JAMA. 2005 Nov 16;294(19):2437-45. doi: 10.1001/jama.294.19.2437. Erratum in: JAMA. 2005 Dec 28;294(24):3092. PMID: 16287954.

3.3.0.1. Fisher's one sided left tailed exact test The hyper-geometric distribution (HGD) describes the probability of x successes in N **draws without replacement** while the same distribution is valid for all sample sizes. In contrast to the hyper-geometric distribution, the binomial distribution describes the probability of x successes in N **draws with replacement** . The one sided left tailed P Value is used when the alternative to independence is that there is a **negative relationship** between the variables investigated. Fisher's exact test (Fisher, 1935b) is a statistical significance test which is based on the hyper-geometric distribution and enable us to calculate the significance of the deviation from a null hypothesis (e.g., P Value) exactly. The left tailed P Value (no replacement, hyper-geometric distribution) (see also Fisher's exact test (see also Barnard, 1945, Boschloo, 1970, Fisher, 1935b)) is calculated as follows:

$$\begin{aligned} p(X \leq a) &= \sum_{i=0}^{a} \frac{\binom{A}{i}\binom{N-A}{B-i}}{\binom{N}{B}} \\ &= \sum_{i=0}^{1176} \frac{\binom{4439}{i}\binom{8888-4439}{2546-i}}{\binom{8888}{2546}} \\ &= 0,0000040509 \\ &= \text{P Value (one sided left tailed)} \end{aligned} \tag{94}$$

Nonetheless, the data of the study which have been published by Pedersen et al. are contradictory. The study design (see also Barukčić, 2019a) of the study proofed to be p(IOI) = 0,212983798 and is very unfair. The data can only be viewed with some restrictions. Further abnormalities in the data presented are apparent. The proportion (a/A) = 26,49 % is implausibly high. The proportion (c / not A) = 30,79 % and is more or less inconsistent with known facts. Based on the data of the study of Pedersen et al. we have to accept that in the total population in about (b/ not B) $\times$ 100 = 51,45 % subjects are exposed to atorvastatin 80 mg or in other words are atorvastatin 80 mg positive. This does not seem to be in line with reality. In total, 2546 events were observed. In the group not exposed to atorvastatin 80 mg 1370 events were observed. The relative risk reduction is RRR = 13,97 % and indicates some benefit for patient treated with atorvastatin 80 mg . However, this seems to be true only superficially. If atorvastatin 80 mg effectively precluded coronary events, then there should not have been a single event in the atorvastatin 80 mg group. However, contrary to all expectations 1176 occurred in the atorvastatin 80 mg group. The exclusion relationship has been calculated as p(EXCL) = 0,86768677 and is not statistically significant (P Value = 0,123933459). All in all, the results based on these data demand us all more or less to consider in greater detail whether atorvastatin 80 mg is of any value in the prevention of any coronary event. It is necessary to note with great regret that

$$\frac{\text{Any coronary event}}{\text{Sample size}} = \frac{\text{Atorvastatin + Simvastatin}}{8888} = \frac{2546}{8888} = 28,6\% \tag{95}$$

Also signalizes us p (EXCL) approx.= 1-(a/A)) > 0,73507547 a 3-hydroxy-3-methylglutaryl-coenzym-A-reductase inhibitor disaster. In other words, more than one in four patients taking atorvastatin or simvastatin still experienced a coronary event. What sense does it make to take these drugs at all? We rightfully expect that simvastatin or atrovastatin reliably exclude or prevent any coronary event. However, this is not the case under any circumstances. Atorvastatin 80 mg does not protect against acute myocardial infarction. Consequently, the question must be asked with great emphasis whether **the lipid hypothesis of atherosclerosis** can still be upheld against the background of the results of these studies?

3.4. Atorvastatin and simvastatin

The study of Terje R Pedersen et al. (see Pedersen and Ideal, 2005) has been unfair and failed to use a suitable placebo group. The data are therefore not utilizable. To address this possible shortcoming, we will compare the data of the study of Terje R Pedersen et al. with a ficitve group of subjects who received a fresh glass of healthy water once a day as medication. We calculate the events in this fictive placebo group according to the placebo group proportions of the Scandinavian Simvastatin Survival Study (see Pedersen and 4S, 1994) as follows, while b=c.

$$\frac{622}{2223} = \frac{6342}{X} \tag{96}$$

and

$$X = NotA = 6342 \times \frac{2223}{622} = 22666 \tag{97}$$

It is d = 22666 - 6342 = 16324 and b+d = 6342 + 16324 = 22666. Table 23 is illustrating this new situation.

Table 23. The relationship between (atorvastatin or simvastatin) and any coronary event (Study of Pedersen et al. , 2005 / Fictive placebo group).

		Any coronary event		
		YES	NO	
(Atorvastatin or Simvastatin)	YES	2546	6342	8888
	NO	6342	16324	22666
		8888	22666	31554

STATISTICAL ANALYSIS.	
Causal relationship k =	0,00665130
P Value (one sided left tailed) (HGD) =	0,88396395
p (EXCL) =	0,91931292
p (EXCL) approx.= 1-(a/A)) >	0,71354635
p (EXCL) approx.= 1-(a/B)) >	0,71354635
P VALUES.	
P Value (one sided left tailed) (HGD) =	0,88396395
$\tilde{\chi}^2$ (EXCL— A_t) =	729,31098110
$\tilde{\chi}^2$ (EXCL— B_t) =	729,31098110
P Value (EXCL) =	0,07751769
PROPORTIONS.	
(a/A) × 100 =	28,65 %
(b/A) × 100 =	71,35 %
(c/ not A) × 100 =	27,98 %
(d/ not A) × 100 =	72,02 %
(a/B) × 100 =	28,65 %
(c/B) × 100 =	71,35 %
(b/ not B) × 100 =	27,98 %
(d/ not B) × 100 =	72,02 %
(A/N) × 100 =	28,17 %
(not A/N) × 100 =	71,83 %
(B/N) × 100 =	28,17 %
(not B/N) × 100 =	71,83 %
ADDITIONAL STATISTICAL MEASURES.	
RELATIVE RISK (RR).	
RR (necessary condition) =	1,02377142
RR (sufficient condition) =	1,02377142
Relative risk reduction (RRR) =	-2,38 %
OTHER STATISTICAL MEASURES.	
Odds ratio (OR) =	1,03331447
Index of relationship (IOR) =	0,01696201
STUDY DESIGN.	
p(IOU)=	0,43664829
p(IOI)=	0,00000000

A stubborn supporter of atorvastatin or simvastatin could make the following counterargument. The c/(Not A) ratio is too much to the disadvantage of atorvastatin or simvastatin and unacceptable in this manner. However, this counterargument is without any effect on the overall result and without any help for atorvastatin or simvastatin. Under fair study conditions, we must ensure that b = c = 6342 as long as this kind of question is investigated. That is, to increase the ratio c/(Not A) = 6342 / 20000 = 31,71 %, we can only decrease the number of subjects in the placebo group (Not A = 20000). However, in this case, the exclusion relationship worsens even more (p (EXCL) = 0,91186652; P Value (EXCL) = 0,08436135) to the disadvantage of atrovastatin or simvastatin (see table 24). Thus far, there is no logical way out other than to recognize that especially under fair study conditions (b=c) simvastatin or atorvastatin does not protect people against coronary events (P Value (EXCL) > 0,0775176).

Table 24. The relationship between atorvastatin or simvastatin and any coronary event (Study of Pedersen et al., 2005 / Fictive placebo group).

		Any coronary event		
		YES	NO	
Atorvastatin or simvastatin	YES	2546	6342	8888
	NO	6342	13658	20000
		8888	20000	28888

STATISTICAL ANALYSIS.	
Causal relationship k =	-0,03064635
P Value (one sided left tailed) (HGD) =	0,00000009
p (EXCL) =	0,91186652
p (EXCL) approx.= 1-(a/A)) >	0,71354635
p (EXCL) approx.= 1-(a/B)) >	0,71354635
P VALUES.	
P Value (one sided left tailed) (HGD) =	0,00000009
$\tilde{\chi}^2$ (EXCL— A_t) =	729,31098110
$\tilde{\chi}^2$ (EXCL— B_t) =	729,31098110
P Value (EXCL) =	0,08436135
PROPORTIONS.	
(a/A) × 100 =	28,65 %
(b/A) × 100 =	71,35 %
(c/ not A) × 100 =	31,71 %
(d/ not A) × 100 =	68,29 %
(a/B) × 100 =	28,65 %
(c/B) × 100 =	71,35 %
(b/ not B) × 100 =	31,71 %
(d/ not B) × 100 =	68,29 %
(A/N) × 100 =	30,77 %
(not A/N) × 100 =	69,23 %
(B/N) × 100 =	30,77 %
(not B/N) × 100 =	69,23 %
ADDITIONAL STATISTICAL MEASURES.	
RELATIVE RISK (RR).	
RR (necessary condition) =	0,90335429
RR (sufficient condition) =	0,90335429
Relative risk reduction (RRR) =	9,66 %
OTHER STATISTICAL MEASURES.	
Odds ratio (OR) =	0,86455581
Index of relationship (IOR) =	-0,06896119
STUDY DESIGN.	
p(IOU)=	0,38465799
p(IOI)=	0,00000000

4. Discussion

Unfortunately, even this publication could not conclusively clarify the fundamental question of whether 3-hydroxy-3-methylglutaryl-coenzym-A-reductase inhibitors (HMGCARI) are useful against coronary events. However, the reasonable doubts about this group of drugs are growing more and more. Even if the assessment of the efficacy of some 3-hydroxy-3-methylglutaryl-coenzym-A-reductase inhibitors in this publication is based on very questionable studies, the data of these studies are not completely out of the air. In other words, and with appropriate limitations, the data from the studies discussed in this publication can more or less be used for further analysis. Remarkably, almost all of the studies presented provide arguments for the use of 3-hydroxy-3-methylglutaryl-coenzym-A-reductase inhibitors as well as against any use of this group of drugs. In particular, the study of Terje R Pedersen et al. [37] is worthy of elementary consideration. A total of 8888 individuals received atorvastatin or simvastatin to prevent any coronary event. Nevertheless, a total of 2546 coronary events occurred in this population besides of the administration of these drugs. The proportion B/N is 2546/8888 = 28,65 %(see Pedersen and Ideal, 2005). In contrast to this result and according to the Scandinavian Simvastatin Survival Study (see Pedersen and 4S, 1994) coronary events occur in a population not exposed to 3-hydroxy-3-methylglutaryl-coenzym-A-reductase inhibitors to an extent of about (c/ (not A)) = (622/2223)×100 = 27,98 % (see table 20). In the group exposed to 3-hydroxy-3-methylglutaryl-coenzym-A-reductase inhibitors **28,65 %** coronary events occurred and thus far much more than in the group not exposed to 3-hydroxy-3-methylglutaryl-coenzym-A-reductase inhibitors (**27,98 %**). This is much more than a devastating result for the 3-hydroxy-3-methylglutaryl-coenzym-A-reductase inhibitors which forces us to raise a number of further questions. Even though only few studies were analyzed as an example, the results obtained are more than disillusioning. In general, 3-hydroxy-3-methylglutaryl-coenzym-A-reductase inhibitors do not reliably protect against any coronary event. As can be expected, a possibly sceptical reader might want to note that the two groups cannot be compared at all. And not only this. Pedersen et al. found that "622 patients (28%) in the placebo group and 431 (19%) in the simvastatin group had one or more major coronary events. "But now, the definition of coronary events is not the same as defined by Pedersen et al. (see Pedersen and Ideal, 2005) in the year 2005. And so on, and so forth. However, all the theoretically conceivable counterarguments do not change the hard data presented. In toto, 8888 subjects (see Pedersen and Ideal, 2005) were treated by atorvastatin or simvastatin but nevertheless 2546 subjects or 28,65 % exposed to artorvastatin or simvastatin still suffered coronary events. In spite of **the lack of a suitable placebo group**, it is possible to calculate the approximate (see Barukčić, 2021a) exclusion relationship (see also table 24) as

$$\text{p(EXCL)}_{\text{approx}} \geq 1-(\frac{B}{N}) = 1-(\frac{2546}{8888}) = 1-0,2865 = 0,7135 \tag{98}$$

In the case that atorvastatin or simvastatin would protect against coronary events with certainty, not a single coronary event would have occurred in this study population (n = 8888). Unfortunately and contrary to any expectation, 2546 coronary events were observed. Even with the very best will in

[37] Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I, Larsen ML, Bendiksen FS, Lindahl C, Szarek M, Tsai J; Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) Study Group. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. JAMA. 2005 Nov 16;294(19):2437-45. doi: 10.1001/jama.294.19.2437. Erratum in: JAMA. 2005 Dec 28;294(24):3092. PMID: 16287954.

the world, this value cannot be considered as persuasive. Of course, we can in no way deny that a myocardial infarction may have several causes. One cause might be plaque rupture, another coronary thrombosis, and another fat embolism (FE) et cetera. Fat embolism or fat embolism syndrome (FES) is a clinical phenomenon which is characterised by systemic dissemination of fat emboli within the system of circulation including coronary arteries fat embolism (CAFE), cerebral arteries fat embolism (CAFE) et cetera. [38] , [39] , [40] In this regard, 3-hydroxy-3-methylglutaryl-coenzym-A-reductase inhibitors could be of use, but a suitable diet or nutritional regime might also be helpful. It remains to be noted that the reputation of 3-hydroxy-3-methylglutaryl-coenzym-A-reductase inhibitors is obviously based more on doubtful study design and even more on dubious statistical methods used to analyze the collected data than on hard facts. One may twist and turn it as one pleases, the confidence in the effectiveness of 3-hydroxy-3-methylglutaryl-coenzym-A-reductase inhibitors to protect people against any coronary event does not seem to be factually justified. At the end of this inquiry, the data presented in this publication do not allow us to conclude otherwise.

5. Conclusion

Atorvastatin and potentially other 3-hydroxy-3-methylglutaryl-coenzym-A-reductase inhibitors does not protect people against acute myocardial infarction.

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6. Patient consent for publication

Not required.

Conflict of interest statement

No conflict of interest to declare.

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Abbreviations

BMI, body mass index; ESRD, end-stage renal disease; HD, hemodialysis; CABG, coronary artery bypass graft; CCI, Charlson comorbidity index; AMI, acute myocardial infarction; MACE, major adverse cardiovascular events; LDL-C, low-density lipoprotein cholesterol; GFR, glomerular filtration rate; STEMI, ST elevation myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; MI, myocardial infarction; ARB, angiotensin receptor blocker; ACEI, angiotensin-converting enzyme inhibitors; CCBs, calcium channel blockers;HMGCARI, 3-hydroxy-3-methylglutaryl-coenzym-A-reductase inhibitor; RR (nc), relative risk (necessary condition); RR (sc), relative risk (sufficient condition); OR, odds ratio; IOR, index of relationship; p(IOU), index of unfairness; p(IOI), index of independence.

Private note

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

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

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