Herpes simplex virus type 1 is the cause of Alzheimer's disease

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Abstract

Objective: The possible involvement of viruses, specifically Herpes simplex virus type 1 (HSV-1), in senile dementia of the Alzheimer type has been investigated by numerous publications. Over 120 publications are providing direct or indirect evidence of a potential relationship between Herpes simplex virus type 1 and Alzheimer's disease (AD) but a causal relation is still not established yet.

Methods: A systematic review and re-analysis of studies which investigated the relationship between HSV-1 and AD by HSV-1 immunoglobulin G (IgG) serology and polymerase chain reaction (PCR) methods was conducted. The method of the conditio sine qua non relationship (SINE) was used to proof the hypothesis: *without* HSV-1 infection of human brain *no* AD. The method of the conditio per quam relationship (IMP) was used to proof the hypothesis: *if* HSV-1 infection of human brain *then* AD. The mathematical formula of the *causal relationship* k was used to proof the hypotheses is, whether there is a cause-effect relationship between HSV-1 and AD. Significance was indicated by a p-value of less than 0.05.

Results: The studies analyzed were able to provide strict evidence that HSV-1 is a necessary condition (a conditio sine qua non), a sufficient condition and a necessary and sufficient condition of AD. Furthermore, the cause-effect relationship between HSV-1 and AD was highly significant.

Conclusions: The data analyzed provide sufficient evidence to conclude that HSV-1 is the cause of AD.

Keywords*: Herpes simplex virus type 1, Alzheimer's disease, causal relationship.*

1. Introduction

Alzheimer's disease (Alzheimer, 1906, 1907) defined by *Alois Alzheimer* (1864-1915) at the "*37. Versammlung Südwestdeutscher Irrenärzte*" or 37th Meeting of South-West German Psychiatrists (Drouin & Drouin, 2017; Hippius & Neundörfer, 2003) held in Tubingen on November 3, 1906 is by far one of the most devastating brain disorders of elderly humans. Alzheimer's disease is a neurodegenerative disorder characterized by a subtle clinical presentation while the progressive decline in cognitive functions is leading to memory loss and dementia. In 2010, about 35.5 million individuals were affected by dementia in the world (Piacentini et al., 2014). More than 20 different risk factors (Henderson, 1988) for Alzheimer's disease, including age, lifestyle, familial inheritance (Kim, Basak, & Holtzman, 2009), exposure to aluminium, traumatic brain injury (TBI), associated vascular and other co-morbidities and infection have been discussed in the literature (Armstrong, 2019) to determine to a high degree the occurrence (Imtiaz, Tolppanen, Kivipelto, & Soininen, 2014) of dementia and Alzheimer's disease, the leading cause of dementia. Especially *Herpes simplex virus type 1*, a highly neurotropic double-stranded DNA virus, is repeatedly implicated in AD pathology by an increasing number of reports. The majority of the world-wide human population is infected with herpes simplex virus type 1. The seroprevalence (Shen et al., 2015) of Herpes simplex virus type 1 (HSV-1) was published as 63.2% and 7.7% for genital herpes, caused usually by Herpes simplex virus type 2 (HSV-2). During a typical primary infection, HSV-1 spreads from the oral pharynx to the trigeminal ganglia, where a latent HSV-1 infection for the entire life of the host is established followed by periodic reactivations. This is not the only path (Burgos, Ramirez, Sastre, Alfaro, & Valdivieso, 2005) through which the reactivated HSV-1 virus may infect the brain (Jamieson, Maitland, Craske, Wilcock, & Itzhaki, 1991; Kastrukoff et al., 1982; Lewandowski, Zimmerman, Denk, Porter, & Prince, 2002; Schmutzhard, 2001) without causing observable neurologic signs. However, a rare but severe and most fatal viral encephalitis can occur too, the Herpes simplex

encephalitis (Sekizawa & Openshaw, 1984; Steiner, 2011). Herpes simplex encephalitis (HSE) is one of the most devastating disorders caused by Herpes simplex. The prognosis of HSE is dependent on early diagnosis and effective therapy. Meanwhile, HSV-1 infection (Ball, 1982) has been linked to Alzheimer's disease (De Chiara et al., 2012; Ruth F. Itzhaki, 2017; Piacentini et al., 2014) too, even if the underlying molecular and functional mechanisms have not been fully elucidated yet. HSV-1 DNA has been discovered to reside in a high proportion of brains of elderly people in latent form (Jamieson, Maitland, Wilcock, Craske, & Itzhaki, 1991) while HSV-1 DNA was present only in a very small proportion of brains of very young people and children (M. A. Wozniak, Mee, & Itzhaki, 2009; Matthew A. Wozniak, Shipley, Combrinck, Wilcock, & Itzhaki, 2005). However, the increase in life expectancy is still regarded as the main risk factor for AD. Neuropathologically, the brain of Alzheimer's disease sufferer is characterized by the presence of extracellular amyloid plaques composed of amyloid-β protein (Aβ) and intraneuronal neurofibrillary tangles composed of hyperphosphorylated Tau protein (Kosik, Joachim, & Selkoe, 1986). People surviving HSE showed clinical signs of AD (i.e., cognitive impairment and memory loss) which provided some evidence suggesting (Ball, 1982) the involvement of HSV-1 in AD. Meanwhile, studies are providing some solid support of the involvement of HSV-1 infection in AD pathogenesis. In Alzheimer's disease brains, Wozniak et al. (M. A. Wozniak et al., 2009) reported that about 90% of the Alzheimer's disease plaques contained the HSV-1 DNA (Matthew A. Wozniak, Frost, & Itzhaki, 2009). Other studies conducted demonstrated the relationship between AD and HSV-1 infection by searching for antibodies (Kobayashi et al., 2013; Letenneur et al., 2008; Mancuso, Baglio, Cabinio, et al., 2014) and other against HSV-1 in the blood of AD patients. Several reviews and meta-analysis.(Harris & Harris, 2018; Ruth F. Itzhaki, 2018a; Steel & Eslick, 2015; Tzeng et al., 2018) investigated whether research data are supporting the hypothesis that brain infections by herpes simplex virus type 1 are causally related with AD and published controversy results. Especially, the 57 studies review and meta-analysis by Warren-Gash et al. (Warren-Gash et al., 2019) found for HSV-1 no evidence that DNA in the brain was associated with dementia though quality across the 57 included studies was very low. Nevertheless, the potential pathogenetic link between HSV1 infection AD remains unclear (Olsson et al., 2016; Pisa, Alonso, Fernández-Fernández, Rábano, & Carrasco, 2017).

2. Material and methods

The studies meta-analyzed preferred to use its own terminology, its own kits, its own primers et cetera to describe scientific discoveries with respect to AD. The results of these studies are aggravated especially by missing a uniform operational definition of HSV-1 positivity and standardization in general. Finally, besides of the use of different methodological approaches and other factors which are a potential source of bias, the studies were able to agree on certain points.

2.1. Material

2.1.1. Search Strategy

Google Scholar and the database PubMed was search for research articles pertaining to infection and AD using some suitable key words like "Herpes simplex type 1", "Alzheimer's disease", PCR or IgG et cetera conducted in any country which investigated the relationship between HSV-1 and AD by polymerase chain reaction (PCR) technology or serum HSV-1 IgG. There was no financial support for this study. Therefore, only studies with data publicly available were formally considered for a review.

In general, *18 PCR based* studies (Beffert, Bertrand, Champagne, Gauthier, & Poirier, 1998; Bertrand, 1993; Cheon, Bajo, Gulesserian, Cairns, & Lubec, 2001; Deatly, Haase, Fewster, Lewis, & Ball, 1990; Hemling et al., 2003, 2003; Itabashi, Arai, Matsui, Higuchi, & Sasaki, 1997; R. F. Itzhaki et al., 1997; Jamieson, Maitland, & Itzhaki, 1992; Jamieson, Maitland, Wilcock, et al., 1991; Kittur et al., 1992; W. R. Lin, Graham, MacGowan, Wilcock, & Itzhaki, 1998; W. R. Lin, Shang, & Itzhaki, 1996; W.-R. Lin, Wozniak, Wilcock, & Itzhaki, 2002; Mori et al., 2004; Olsson et al., 2016; Roberts et al., 1986; M. A. Wozniak et al., 2009) were identified, while the study design of almost all PCR based studies was very inappropriate. IgG seropositivity was studied by *15* studies, including the studies of Barnes et al. and Wozniak et al. (Barnes et al., 2015; Matthew A. Wozniak et al., 2005).

Table 1. ***The article selection process of the studies analyzed***

1. Identification of records	Size	Total
Records identified by searching in the databases		
PubMed	137	
Google Scholar	958	
Additional records identified from review articles		
Harris and Harris, 2018	278	
Warren-Gash et al., 2019	83	1456
2. Clean-up of search (Screening)		
Records removed after verifying duplication, excluded by title, excluded due to other reasons		1423
3. Eligibility		
Articles evaluated for eligibility		33
Articles excluded for various reasons		
- Data were self-contradictory	6	
- Data are not appropriate enough	4	
- Data access barriers	13	
4. Included		
Articles included in the meta-analysis (**Table 2, 4, 5, 6**)		10

Adopted from PRISMA 2009 (Moher, Liberati, Tetzlaff, & Altman, 2009).

2.1.2. HSV-1 IgG-Studies considered for re-analysis

The following HSV-1 IgG sero-epidemiological studies (Agostini, Mancuso, Baglio, Cabinio, Hernis, Guerini, et al., 2016, 2016; Letenneur et al., 2008; Lövheim, Gilthorpe, Adolfsson, Nilsson, & Elgh, 2015; Lövheim, Gilthorpe, Johansson, et al., 2015; Mancuso, Baglio, Agostini, et al., 2014; Mancuso, Baglio, Cabinio, et al., 2014) as presented by **Table** 2 were considered for meta-analysis.

Table 2. ***Without*** **HSV-1 IgG sero-positivity** ***no*** **AD**.

Study ID	Year	N	Case_P (a)	Case_T (a+c)	Con_P (b)	Con_T (b+d)	p(SINE)	X^2(SINE|Bt)	X^2(SINE|$\underline{A}$t)	k	P value (k)	IOU	IOI
Letenneur et al.	2008	490	69	77	335	413	0,984	0,831	0,744	0,081	0,026	0,018	0,667
Lövheim et al.	2014	3432	213	227	2813	3205	0,996	0,863	0,483	0,047	0,001	0,052	0,816
Mancuso et al.	2014	134	81	83	50	51	0,985	0,048	1,333	-0,015	0,443	0,597	0,358
Mancuso et al.	2014	157	83	83	71	74	1,000	0,000	0,000	0,148	0,064	0,510	0,452
Lövheim et al.	2015	720	338	360	324	360	0,969	1,344	8,345	0,071	0,018	0,419	0,419
Agostini et al.	2016	120	57	59	60	61	0,983	0,068	1,333	-0,056	0,372	0,467	0,483
Total		5053	841	889	3653	4164		**3,155**	**12,238**			0,344	0,533
				Alpha =			0,050						
				Degrees of freedom =			6						
				Chi square (critical) =			**12,592**						
				Chi square (calculated) =				**3,155**	**12,238**				

Case_P: case, positive; Case_T: case total; Con_P: healthy control positive; Con_T: healthy control total.

The studies of Manusco et al. (Mancuso, Baglio, Cabinio, et al., 2014) and Agostini et al. (Agostini, Mancuso, Baglio, Cabinio, Hernis, Guerini, et al., 2016) were considered for meta-analysis in this context although the study design of both studies was very problematic. Several HSV-1 IgG and other HSV IgG studies (Agostini, Mancuso, Baglio, Cabinio, Hernis, Costa, et al., 2016; Agostini et al., 2018; Barnes et al., 2015; Bu et al., 2015; Féart et al., 2011; Kobayashi et al., 2013; Ounanian, Guilbert, Renversez, Seigneurin, & Avrameas, 1990; Pandey et al., 2019; Matthew A. Wozniak et al., 2005) were not considered for meta-analysis, while some of those studies are viewed by **Table 3**. Several studies had data access barriers, provided inappropriate data or provided self-contradictory data (I. Barukčić, 2019c).

Table 3. HSV-1 IgG studies not considered for re-analyses.

Study ID	Year	N	Case_P (a)	Case_T (a+c)	Con_P (b)	Con_T (b+d)
Bu et al.	2015	263	0	128	0	135
Ounanian et al.	1990	40	0	19	0	21
Pandey et al.	2019	93	0	56	0	37
Agostini et al.	2016	0	0	0	0	0
Barnes et al.	2015	0	0	0	0	0
Féart et al.	2011	0	0	0	0	0
Kobayashi et al.	2013	0	0	0	0	0

2.1.3. PCR-Studies considered for meta-analysis

Studies which detected HSV-1 DNA in postmortem brain tissues from patients with AD and controls (non-neurological cases) by polymerase chain reaction (PCR) methods used different primers (glycoprotein D protein; thymidine kinase) for PCR. The quality of the source of amplification template was different. Rodriguez et al. (Rodriguez, Royall, Daum, Kagan-Hallet, & Chambers, 2005) were able to provide evidence that DNA integrity decreases significantly with increasing time of storage in formalin. Due to this and other factors, PCR studies had very different HSV-1 detection rates. Hemling et al. (Hemling et al., 2003) and Marques et al. (Marques et al., 2001) detected HSV-1 DNA in a very low proportion of brains due to unknown reasons while the access to the data of the study of Marques et al. (Marques et al., 2001) was not possible. Besides of an inappropriate study design, it was possible to calculate the conditio sine qua non relationship of the studies of Jamieson et al. (Jamieson, Maitland, Craske, et al., 1991; Jamieson, Maitland, Wilcock, et al., 1991) and Cheon et al. (Cheon et al., 2001). However, besides of the difficulties mentioned, to many studies were able to provide the impressive detection rates. The PCR studies (Cheon et al., 2001; Jamieson et al., 1992; Jamieson, Maitland, Wilcock, et al., 1991; Mori et al., 2004) which supported the *conditio sine qua non relationship* between HSV-1 and AD are listed by the following table (**Table 4**).

Table 4. *Without* HSV-1 PCR DNA positivity *no* AD (according to PCR studies).

Study ID	Year	N	Case_P (a)	Case_T (a+c)	Con_P (b)	Con_T (b+d)	p(SINE)	X^2(SINE|Bt)	k	IOU	IOI
Jamieson et al.	1992	36	14	21	9	15	0,806	2,333	+0,068	0,222	0,056
Mori et al.	**2004**	**9**	**3**	**3**	**1**	**6**	**1,000**	**0,000**	**+0,791**	**0,222**	**0,111**
Jamieson et al.	1991	14	8	8	6	6	1,000	0,000	-	0,571	0,429
Cheon et al.	2001	20	10	10	10	10	1,000	0,000	-	0,500	0,500

The PCR studies (Cheon et al., 2001; Jamieson et al., 1992; Jamieson, Maitland, Wilcock, et al., 1991; Mori et al., 2004) which provided evidence of a *conditio per quam relationship* between HSV-1 and AD are listed by the following table (**Table 5**).

Table 5. ***If*** **HSV-1 PCR DNA positivity** ***then*** **AD (according to PCR studies)**.

Study ID	Year	N	Case_P (a)	Case_T (a+c)	Con_P (b)	Con_T (b+d)	p(IMP)	X^2(IMP|At)	k	IOU	IOI
Itabashi et al.	1997	**69**	14	46	5	23	0,928	1,316	+0,092	0,058	0,391
Mori et al.	2004	**9**	3	3	1	6	0,889	0,250	+0,791	0,222	0,111

The study of Mori et. al., (2004)

The only PCR based study which provided evidence of a conditio sine qua non relationship, of conditio per quam relationship, of a conditio sine qua non and conditio per quam relationship and of a significant cause effect relationship was the study of Mori et al. (Mori et al., 2004). The sample size was n = 9 and the P value was calculated according to Fisher's exact test (**Table 6**).

Table 6. The study of Mori et. al., (2004).

		Alzheimer's disease		
		Yes	No	
HSV-1 (PCR DNA)	Yes	3	**1**	4
	No	**0**	5	5
		3	6	9

Statistical analysis (Table 6).

Causal relationship k =	**+0,791**	95 % CI (k): (0,045 -	1,000)	IOU =	-0,222
P value (k | Fisher's test) =	**0,04762**	Chi Sq.(k) =	5,625	IOI =	0,111
				p(IOU) + p(IOI)=	**0,333**
p (SINE) =	1,000	Chi Sq. 1(SINE) =	**0,000**	Chi Sq. 2(SINE) =	**0,000**
p (IMP) =	0,889	Chi Sq. 1(IMP) =	**0,167**	Chi Sq. 2(IMP) =	**0,250**
p (SINE ^ IMP) =	0,889	Chi Sq. 1(SINE ^IMP) =	**0,167**	Chi Sq. 2(SINE ^IMP) =	**0,250**
p (EXCL) =	0,667	Chi Sq. 1(EXCL) =	3,000	Chi Sq. 2(EXCL) =	2,250

2.2. Methods

2.2.1. Definitions

Definition 1. (The 2x2 Table)

Karl Pearson (K. Pearson, 1904) introduced in 1904 the notion of a contingency table (I. Barukčić, 2019a, 2019d) or two by two table. Especially the relationships between Bernoulli (i. e. Binomial) distributed random variables can be examined by contingency tables. Thus far, let a Bernoulli distributed random variable A_t occur/exist et cetera with the probability $p(A_t)$ at the Bernoulli trial (period of time) t. Furthermore, let another Bernoulli distributed random variable B_t occur/exist et cetera with the probability $p(B_t)$ at the same Bernoulli trial (period of time) t. Let $p(a_t)= p(A_t \cap B_t)$ denote the joint probability distribution of A_t and B_t at the same Bernoulli trial (period of time) t. The following table (**Table 7**) may show the relationships in more details.

Table 7. The probabitlities of a contingency table

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

In this context, it is *per definitionem*

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

while +1 may denote *the normalized sample space* of A_t and B_t. Under circumstances were *the probability of an event is* ***constant*** *from trial to trial* (i. e. Binomial distribution), the relationships above simplifies. It is *per definitionem*

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

The meaning of the abbreviations a, b, c, d, n et cetera are explained by following 2 by 2-table (**Table 8**). The relationships are valid even under conditions where n = 1.

Table 8. The sample space of a contingency table

		Conditioned B (Outcome)		
		Yes = +1	**No = +0**	**Total**
Condition A (risk factor)	Yes =+1	a	b	A
	No = +0	c	d	$\underline{A}$
	Total	B	$\underline{B}$	*n*

Definition 2. (Index of unfairness)

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

$$IOU \equiv \left(\left(\frac{A + B}{n}\right) - 1\right) \tag{3}$$

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

Definition 3. (The probability of an index of unfairness)

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

$$p(IOU) \equiv Absolute\left(\left(\frac{A + B}{n}\right) - 1\right) \tag{4}$$

Definition 4. Index of independence (IOI)

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

$$IOI \equiv \left(\left(\frac{A + \underline{B}}{n}\right) - 1\right) \tag{5}$$

Definition 5. (The probability of an index of independence)

The probability of an index of independence p(IOI) is defined (I. Barukčić, 2019b) as

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

Definition 6. Sufficient Condition (Conditio per Quam)

The *sufficient* condition (I. Barukčić, 2018d, 1989, 1997, 2017, 2018a, 2018b, 2019d; K. Barukčić & Barukčić, 2016, 2016) relationship (*conditio per quam*) of a population is defined (I. Barukčić, 2019a, 2019d) as

$$\begin{aligned} p(A_t \rightarrow B_t) &\equiv \frac{(a_t) + (c_t) + (d_t)}{N_t} = 1 \\ &\equiv p(a_t) + p(c_t) + p(d_t) \\ &\equiv p(B_t) + p(d_t) \\ &\equiv p(a_t) + p(\underline{A}_t) \\ &\equiv +1. \end{aligned} \tag{7}$$

and is used to prove the hypothesis: *if* A_t *then* B_t or is taken to express that *the occurrence of an event* A_t *is a sufficient condition for existence or occurrence of an event* B_t. Sufficient and necessary conditions are converse relations (I. Barukčić, 2019a, 2019d).

Definition 7. The X^2 Test of Goodness of Fit of a Sufficient Condition

Under certain circumstances, the X^2 test of goodness-of-fit is an appropriate method for testing the null hypothesis that a random sample of observations comes from a specific distribution (i.e. the distribution of a sufficient condition) against the alternative hypothesis that the data have some other distribution (I. Barukčić, 2019a, 2019d). The additive property of X^2 distribution is of special importance in this context. The applicability of using the Pearson chi-squared statistic including Yate's continuity correction (I. Barukčić, 2019a, 2019d) are widely

discussed in literature. Especially, the need of incorporating Yate's continuity correction into the calculation of the X^2 value is very controversial. Thus far, only due to formal reasons, in the following, the use of *the continuity correction* is assured. The chi-square value of a conditio per quam relationship is derived (I. Barukčić, 2019a, 2019d) as

$$X^2\left((A \rightarrow B)|A\right) \equiv \frac{\left((b) - (1/2)\right)^2}{A} + 0 = 0 \tag{8}$$

or alternatively as

$$X^2\left((A \rightarrow B)|\underline{B}\right) \equiv \frac{\left((b) - (1/2)\right)^2}{\underline{B}} + 0 = 0 \tag{9}$$

Definition 8. Necessary Condition (Conditio Sine Qua Non)

The self-organization of matter is governed by view basic natural laws among those is the necessary condition (conditio sine qua non) too. An event A_t which is necessary (or an essential) for some other event B_t to occur must be satisfied in order to obtain B_t (I. Barukčić, 2019a, 2019d). In this respect, let an event A_t with its own probability $p(A_t)$ at the (period of) time *t* be a necessary condition for another event B_t with its own probability $p(B_t)$. This is equivalent to say that it is impossible to have B_t without A_t. In other words, *without* A_t *no* B_t or the absence of A_t must guarantee the absence of B_t. The mathematical formula of the *necessary* condition (I. Barukčić, 2018d, 1989, 1997, 2017, 2018a, 2018b, 2019d; K. Barukčić & Barukčić, 2016, 2016) relationship (conditio sine qua non) of a population is defined (I. Barukčić, 2019a, 2019d) as

$$\begin{aligned} p(A_t \leftarrow B_t) &\equiv \frac{(a_t) + (b_t) + (d_t)}{N_t} = 1 \\ &\equiv p(a_t) + p(b_t) + p(d_t) \\ &\equiv p(A_t) + p(d_t) \\ &\equiv p(a_t) + p(\underline{B_t}) = p(a_t) + \left(1 - p(B_t)\right) \\ &\equiv +1. \end{aligned} \tag{10}$$

Definition 9. The X^2 Test of Goodness of Fit of a Necessary Condition

The chi-square value of a *conditio sine qua non* distribution (I. Barukčić, 2019a, 2019d) before changes to

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

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

$$X^2\left((A \leftarrow B)|\underline{A}\right) \equiv \frac{\left((c) - (1/2)\right)^2}{\underline{A}} + 0 = 0 \tag{12}$$

Definition 10. (The Binomial distribution)

The binomial distribution was derived by the prominent Suisse mathematician Jacob Bernoulli (1655 - 1705) in his work *Ars Conjectandi* (Bernoulli, 1713). Assume a binomial experiment while each experiment is called a Bernoulli trial *t* with repeated trials yielding only two possible outcomes: success, S = +1 or failure, F = +0 while the values of $\pi(x_t)$ and $q(x_t) = (1- \pi(x_t))$ may remain unchanged throughout each trial. The probability of success in the population is π and the probability of failure in the population is $q(x_t) = (1- \pi(x_t))$. Let the binomial random variable X denote the number of successes in *n* such Bernoulli trials, where X = 0, 1, 2, 3, ... , n. The expected value of the binomial random variable X is

$$E(X\ ) \quad = \quad E(x_1 + \cdots + x_n) \quad = E(x_1) + \cdots + E(x_n) \quad = \quad \underbrace{(1 + \cdots + 1) \times \pi(x_t)}_{n\ times} \quad = \quad n \times \pi(x_t) \tag{13}$$

The variance of the binomial random variable X is $\sigma(X)^2 = n \times \pi(x_t) \times (1 - \pi(x_t))$.

Proof.

Since $\sigma(x_t)^2 = \pi(x_t) \times (1 - \pi(x_t))$, we get:

$$\sigma(X\ )^2 \quad = \quad \sigma(x_1 + \cdots + x_n)^2 \quad = \underbrace{\sigma(x_1)^2 + \cdots + \sigma(x_n)^2}_{n\ times} \quad = \quad n \times \sigma(x_t)^2 \quad = \quad n \times \pi(x_t) \times \big(1 - \pi(x_t)\big) \tag{14}$$

Q. e. d.

The sample proportion or the relative frequency of an event $p(x_t) = (x / n)$ is the number x of times the event occurred in an experiment or study of *the sample size n* while $x = x_1 + \cdots + x_n$ where all x_t are independently distributed Bernoulli random variables.

$$E\left(\frac{x}{n}\right) \quad = \quad E\big(p(x_t)\big) \quad = \quad \frac{E(X)}{n} \quad = \quad \frac{1}{n} \times n \times \pi(x_t) \quad = \quad \pi(x_t) \tag{15}$$

and the sample variance is defined as

$$\sigma\left(\frac{x}{n}\right)^2 \quad = \quad \sigma\big(p(x_t)\big)^2 \quad = \quad \frac{\sigma(x)^2}{n^2} \quad = \quad \frac{n \times \pi(x_t) \times \big(1 - \pi(x_t)\big)}{n \times n} \quad = \quad \frac{\pi(x_t) \times \big(1 - \pi(x_t)\big)}{n} \tag{16}$$

Let p(X = x) denote the probability mass function of observing exactly *x* successes in *n* trials, with the probability of success on a single trial denoted by $\pi(x_t)$ and $q(x_t) = 1- \pi(x_t)$ is defined as

$$\mathrm{p}(X = x) \quad = \quad \left(\frac{n!}{x! \times (n - x)!}\right) \pi(x_t)^x \times \big(1 - \pi(x_t)\big)^{n-x} \tag{17}$$

In a slightly different way, the definition of binomial distribution does not rule out another distribution derived from the same. Facts taken together suggest the following form derived from the Bernoulli distribution as

$$\mathrm{p}(X = x) \quad = \quad \left(\frac{n!}{(x + 1)! \times \big(n - (x + 1)\big)!}\right) \big(\pi(x_t)\big)^x \times \big(1 - \pi(x_t)\big)^{n-x} \tag{18}$$

A binomial distribution with parameters $\pi(x_t)$ and n = 1 is called the *Bernoulli distribution* too while x can take the values either +0 or +1. It is

$$\mathrm{p}(X = x) \quad = \quad \big(1 - q(x_t)\big)^x \times \big(1 - \pi(x_t)\big)^{1-x} \tag{19}$$

Under conditions where **X = 0**, the binomial distributions changes to

$$\begin{aligned} \mathrm{p}(X = 0) \quad &= \quad \left(\frac{n!}{x! \times (n - x)!}\right) \big(1 - q(x_t)\big)^x \times \big(1 - \pi(x_t)\big)^{n-x} \\ &= \left(\frac{n!}{0! \times (n - 0)!}\right) \big(1 - q(x_t)\big)^0 \times \big(1 - \pi(x_t)\big)^{n-0} = \big(1 - \pi(x_t)\big)^n \end{aligned} \tag{20}$$

CLAIM.

The *proportion or the probability* $\pi(x_t)$ is given by the formula:

$$\pi(x_t) = e^{-\left(\frac{E(\underline{X}_t)}{n}\right)} \tag{21}$$

PROOF.

In general, it is

$$\pi(x_t) = \pi(x_t) \tag{22}$$

or equally

$$\pi(x_t) = \pi(x_t)^{\frac{\boldsymbol{n}}{\boldsymbol{1}}\times\frac{\boldsymbol{1}}{\boldsymbol{n}}} \tag{23}$$

In particular, it is $\pi(x_t) = 1 - q(x_t)$. Substituting, we obtain

$$\pi(x_t) = \left(\boldsymbol{1} - \boldsymbol{q}(\boldsymbol{x_t})\right)^{n\times\frac{1}{n}} \tag{24}$$

or

$$\pi(x_t) = \left(1 - \frac{\boldsymbol{n} \times q(x_t)}{\boldsymbol{n}}\right)^{n\times\frac{1}{n}} \tag{25}$$

It is $E(\underline{X}) = n\times q(x_t)$. The equation before simplifies as

$$\pi(x_t) = \left(1 - \frac{\boldsymbol{E}(\underline{\boldsymbol{X}})}{n}\right)^{n\times\frac{1}{n}} \tag{26}$$

Increasing the number of randomly generated variables (sample size *n* grows) enable us to take the limit. In point of fact, taking the limit as the number of (Bernoulli) trials or the sample size *n* goes to positive infinity ($n \to +\infty$), we obtain

$$\left(1 - \left(\frac{E(\underline{X})}{n}\right)\right)^{n} = \lim_{n\to+\infty}\left(\left(1 - \left(\frac{E(\underline{X})}{n}\right)\right)^{n}\right) \tag{27}$$

According to the known elementary calculus (DeGroot, Schervish, Fang, Lu, & Li, 2005) it is

$$\lim_{n\to+\infty}\left(\left(1 - \left(\frac{E(\underline{X})}{n}\right)\right)^{n}\right) = e^{-\left(\frac{E(\underline{X})}{1}\right)} \tag{28}$$

as the sample size increases or as the number of trials *n* goes to positive infinity ($n \to +\infty$) the equation above simplifies as

$$\pi(x_t) = e^{-\left(\frac{E(\underline{X})}{n}\right)} \tag{29}$$

QUOD ERAT DEMONSTRANDUM.

Under some circumstances, the P Value ($X \leq$ n-1) can be calculated as

$$p(X \leq \mathrm{n} - 1) \equiv 1 - e^{-\left(\frac{E(\underline{X})}{n}\right)} \tag{30}$$

CLAIM.

The *proportion of X=n events* is given by the function:

$$p\ (X = n) \quad = \quad 1^n \quad = \quad +1 \tag{31}$$

PROOF.

The binomial distribution is defined as

$$\mathrm{p}(X = x) \quad = \quad \left(\frac{n!}{x! \times (n-x)!}\right) \left(\pi(x_t)\right)^x \times \left(1 - \pi(x_t)\right)^{n-x} \tag{32}$$

Under circumstances where X = n, we obtain

$$\mathrm{p}(X = \mathrm{n}) \quad = \quad \left(\frac{n!}{\mathrm{n}! \times (n-n)!}\right) \left(\pi(x_t)\right)^n \times \left(1 - \pi(x_t)\right)^{n-\mathrm{n}} \tag{33}$$

or

$$\mathrm{p}(X = \mathrm{n}) \quad = \quad \left(\pi(x_t)\right)^n \tag{34}$$

or in other words

$$\mathrm{p}(X = \mathrm{n}) \quad = \quad \underbrace{\pi(x_t) \times \ldots \times \pi(x_t)} \quad = \quad \pi(x_t)^n \tag{35}$$

However, the probability of the conditio per quam relationship, of the exclusion relationship, of the necessary and sufficient condition relationship, of *the conditio sine qua non relationship* et cetera is $\pi(x_t) = 1$. In general, we obtain

$$\mathrm{p}(X = \mathrm{n}) \quad = \quad \underbrace{\pi(x_t) \times \ldots \times \pi(x_t)} \quad = \quad \pi(x_t)^n \quad = \quad 1^n \quad = \quad 1 \tag{36}$$

QUOD ERAT DEMONSTRANDUM.

Definition 11. (Left tailed one-sided P value)

CLAIM.

The left sided P value follows as

$$p(X \leq \mathrm{n} - 1) \quad \equiv \quad 1 \quad - \quad e^{-\frac{E(X)}{n}} \tag{37}$$

PROOF.

It is

$$p(X \leq \mathrm{n} - 1) \quad + \quad p(X > \mathrm{n} - 1) \quad \equiv \quad 1 \tag{38}$$

However, the only value where (X > n-1) is the value (X=n). Therefore, the probabilities are equal or it is p(X > n-1) = p(X=n). The equation before changes to

$$p(X \leq \mathrm{n} - 1) \quad + \quad p(X = \mathrm{n}) \quad \equiv \quad 1 \tag{39}$$

or

$$p(X \leq \mathrm{n} - 1) \quad = \quad 1 \quad - \quad p(X = \mathrm{n}) \tag{40}$$

As proofed before, it is

$$p(X = \mathrm{n}) \quad = \quad \pi(x_t) \quad = \quad e^{-\left(\frac{E(X)}{n}\right)} \tag{41}$$

Under these conditions, the left sided P value follows as

$$p(X \leq \mathrm{n} - 1) \quad \equiv \quad 1 \quad - \quad e^{-\frac{E(X)}{n}} \tag{42}$$

QUOD ERAT DEMONSTRANDUM.

Definition 12. The approximate probability of the necessary condition in the population

Let x_t denote a Bernoulli distributed random variable with its own boolean-valued outcome each asking a yes–no question of *either* (success or yes or true or +1) with probability $p(x_t)$ *or* (failure or no or false or +0) with probability $q(x_t) = 1 - p(x_t)$. Let the *probability or the proportion of an event within the population* denoted as $\pi(x_t)$. Let a single success/failure experiment call a *Bernoulli trial t* or Bernoulli experiment and a sequence of outcomes is a Bernoulli process and at the end the sample size *n*.

CLAIM.

The *probability or the proportion of an event within the population* denoted as $\pi(x_t)$ is determined by the number of missed successes $E(\underline{X}) = n - E(X) = 0, 1, 2, ..., n$ in *n* trials and can be calculated by the formula

$$\pi(x_t) = 1 - \left(\frac{E(\underline{X})}{E(X)}\right) \times e^{-\left(\frac{E(\underline{X})}{n}\right)} \tag{43}$$

PROOF.

In general, we expect the probability or the population proportion of a binomial distributed random variable in the population, $\pi(x_t)$, is constant from trail to trial and independent of the number of trials performed or it is

$$\pi(x_t) = \pi(x_t) \tag{44}$$

Thus far it is equally valid that

$$\pi(x_t) = \pi(x_t) - 1 + 1 \tag{45}$$

or at the end

$$\pi(x_t) = 1 - \left(1 - \pi(x_t)\right) \tag{46}$$

Rearranging, we obtain

$$\pi(x_t) = 1 - \frac{\boldsymbol{n \times \pi(x_t)} \times \left(1 - \pi(x_t)\right)}{\boldsymbol{n \times \pi(x_t)}} \tag{47}$$

or

$$\pi(x_t) = 1 - \frac{n \times \left(1 - \pi(x_t)\right)}{n \times \pi(x_t)} \times \pi(x_t) \tag{48}$$

With respect to the population, it is $E(X) = n \times \pi(x_t)$ and $E(\underline{X}) = n \times (1 - \pi(x_t)) = n \times q(x_t)$. The equation before changes to

$$\pi(x_t) = +1 - \frac{E(\underline{X})}{E(X)} \times \pi(x_t) \tag{49}$$

Mathematically, this equation is equivalent with

$$\pi(x_t) = +1 - \frac{E(\underline{X})}{E(X)} \times \pi(x_t)^{\frac{\boldsymbol{n}}{\boldsymbol{1}} \times \frac{\boldsymbol{1}}{\boldsymbol{n}}} \tag{50}$$

In general, it is $\pi(x_t) = 1 - q(x_t)$. Substituting, we obtain

$$\pi(x_t) = +1 - \left(\frac{E(\underline{X})}{E(X)}\right) \times \left(\left(\boldsymbol{1 - q(x_t)}\right)^{\frac{n}{1} \times \frac{1}{n}}\right) \tag{51}$$

or

$$\pi(x_t) = +1 - \left(\frac{E(\underline{X})}{E(X)}\right) \times \left(\left(1 - \frac{\boldsymbol{n} \times q(x_t)}{\boldsymbol{n}}\right)^{\frac{n}{1} \times \frac{1}{n}}\right) \tag{52}$$

or

$$\pi(x_t) = +1 - \left(\frac{E(\underline{X}\ )}{E(X\ )}\right) \times \left(\left(1 - \frac{E(\underline{X}\ )}{n}\right)^{\frac{n}{1} \times \frac{1}{n}}\right) \tag{53}$$

Taking the limit as the sample size n or the number of (Bernoulli) trials goes to positive infinity ($n \to +\infty$), we obtain

$$\left(1 - \left(\frac{E(\underline{X}\ )}{n}\right)\right)^{n} = \lim_{n \to +\infty} \left(\left(1 - \left(\frac{E(\underline{X}\ )}{n}\right)\right)^{n}\right) \tag{54}$$

According to the known elementary calculus (DeGroot et al., 2005) it is

$$\lim_{n \to +\infty} \left(\left(1 - \left(\frac{E(\underline{X}\ )}{n}\right)\right)^{n}\right) = e^{-\mathrm{E}(\underline{X}\ )} \tag{55}$$

Thus far, as the sample size increases or as the number of trials n goes to positive infinity ($n \to +\infty$) the equation above simplifies as

$$\pi(x_t) = +1 - \left(\left(\frac{E(\underline{X}\ )}{E(X\ )}\right) \times \left(e^{-\frac{E(\underline{X}\ )}{n}}\right)\right) \tag{56}$$

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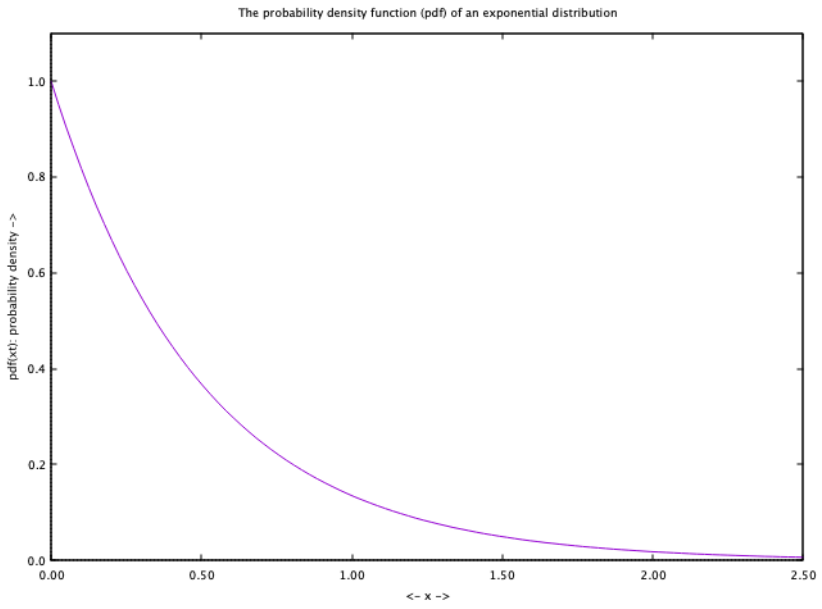

Figure 1. Example exponential distribution

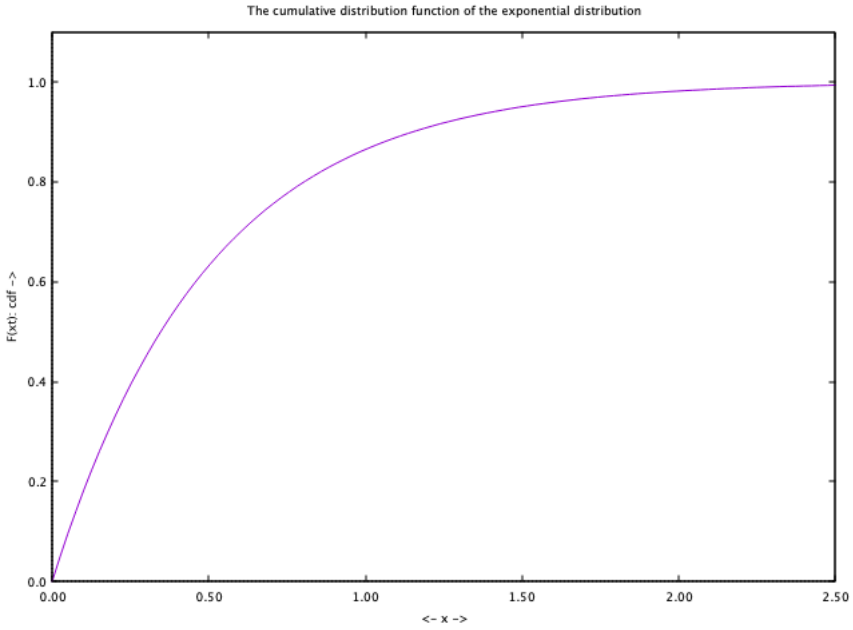

Figure 2. Example cumulative distribution function of the exponential distribution

Definition 13. (Left tailed one-sided P value according to exponential distribution)

Increasing sample size, it is possible to detect small effects, even though they are not existent in population. The chi square distribution finds its own limits if the sample size is to large or too small. *Fisher's exact test* (Agresti, 1992; R. A. Fisher, 1922; Ronald A. Fisher, 1925) is valid for all sample sizes although in practice it is used when sample sizes are small. The Chi-square (Karl Pearson, 1900) itself is very *sensitive* (Bergh, 2015) to sample size and an extremely large sample is one of the *limitations* (McHugh, 2013) of a Chi-square test. Alternatives to the Chi-Square Test for extremely large samples like *the G-square test* (Sokal & Rohlf, 1995) have been developed to handle large samples in test of fit analysis. However, Chi-square is still reliable with sample size between roughly 100 to 2500 subjects. An exact binomial test can be used when an experiment has two possible outcomes (i.e. success/failure) instead of the chi-square distribution to compare the observed distribution to the expected distribution. The null hypothesis for the binomial test is that the results observed (p(sample proportion)) do not differ significantly from what is expected to be in the population ($\pi = 1$). The (*left* tailed) one-sided null and alternative hypotheses may be as follows:

$$\begin{aligned} H_0: \quad & \pi(population) \quad \leq \quad p(sample\ proportion) \quad (i.e.\ SINE\ relationship: \text{NO}) \\ H_A: \quad & \pi(population) \quad > \quad p(sample\ proportion) \quad (i.e.\ SINE\ relationship: \text{YES}) \end{aligned} \tag{57}$$

How likely is it that an observed difference from what is expected to be is only due to chance? Folowing the Fisherian and Neyman-Pearsonian schools of hypothesis testing the calculation of the P value (Arbuthnott, 1710; Ronald A. Fisher, 1925; Heyde & Seneta, 2001; LaPlace, Pierre Simon de, 1812; Karl Pearson, 1900) can answer questions like these. Since Fisher's statement years ago, it has become ritualistic by medical researchers worldwide to use 0.05 as cut-off for a P value. However, after the advent of computers and statistical software, calculating exact P values is easy now and so the researcher can report exact P values and leave it to a reader to determine the significance of the same. In point of fact, P value being a probability can take any value between 0 and 1. Thus far, P values close to 1 suggests no difference between what is observed from what is expected to be due to chance whereas P values close to 0 indicate that a difference observed is unlikely to be due to chance. However, like the test of hypothesis, the P value itself is associated with several *fallacies* (Dahiru, 2008) and depends on several factors, among other on *the distribution used*. P values alone can completely misrepresent (Bertolaccini, Viti, & Terzi, 2016; Dixon, 2003) the evidence provided by sample data and an alternative analytical technique is

necessary to be developed. In general, the P value is *the probability of an outcome*, when the null hypothesis is true, which is at least as extreme as the observed.

CLAIM.

The (*left*-tailed one-sided) P value can be calculated as

$$p\big(X \leq (\mathrm{n}-1)\big) \equiv \left(\left(\frac{E\big(\underline{X}\ \big)}{E(X\ )}\right) \times \left(e^{-\frac{E(\underline{X}\ )}{n}}\right)\right) \tag{58}$$

PROOF.

In general, it is

$$+1 \equiv p\big(X < (\mathrm{n}-1)\big) + p\big(X = (\mathrm{n}-1)\big) + p\big(X > (\mathrm{n}-1)\big) \tag{59}$$

or

$$+1 \equiv p\big(X \leq (\mathrm{n}-1)\big) + p\big(X > (\mathrm{n}-1)\big) \tag{60}$$

or

$$p\Big(\big(X \leq (\mathrm{n}-1)\big)\Big) \equiv 1 - p\Big(\big(X > (\mathrm{n}-1)\big)\Big) \tag{61}$$

Mathematically, the only value where **(X > (n-1))** is **X = x = n.** Under these conditions, the probabilities are equal or it is **p(X>(n-1))= p(X=n).** The equation before changes to

$$p\Big(\big(X \leq (\mathrm{n}-1)\big)\Big) \equiv 1 - p\Big(\big(X = (\mathrm{n})\big)\Big) \tag{62}$$

As proofed before, in this case we obtain

$$p(X = \mathrm{n}) = +1 - \left(\left(\frac{E\big(\underline{X}\ \big)}{E(X\ )}\right) \times \left(e^{-\frac{E(\underline{X}\ )}{n}}\right)\right) \tag{63}$$

This formula derived before is valid even for random variables where X =n. Substituting this relationship into the equation before, we obtain

$$p\Big(\big(X \leq (\mathrm{n}-1)\big)\Big) \equiv 1 - \left(1 - \left(\left(\frac{E\big(\underline{X}\ \big)}{E(X\ )}\right) \times \left(e^{-\frac{E(\underline{X}\ )}{n}}\right)\right)\right) \tag{64}$$

The P value can be calculated according to the equation before (for *very large samples* too) were π is expected to be 1. A *left tailed* ***P value*** **which is** ***greater than or equal*** **to α** (P value ≥ α) provides some evidence (Yamane, 1964) to ***accept the null hypothesis*** otherwise not. Simplifying equation, the left tailed P value follows as

$$p\Big(\big(X \leq (\mathrm{n}-1)\big)\Big) \equiv \left(\left(\frac{E\big(\underline{X}\ \big)}{E(X\ )}\right) \times \left(e^{-\frac{E(\underline{X}\ )}{n}}\right)\right) \tag{65}$$

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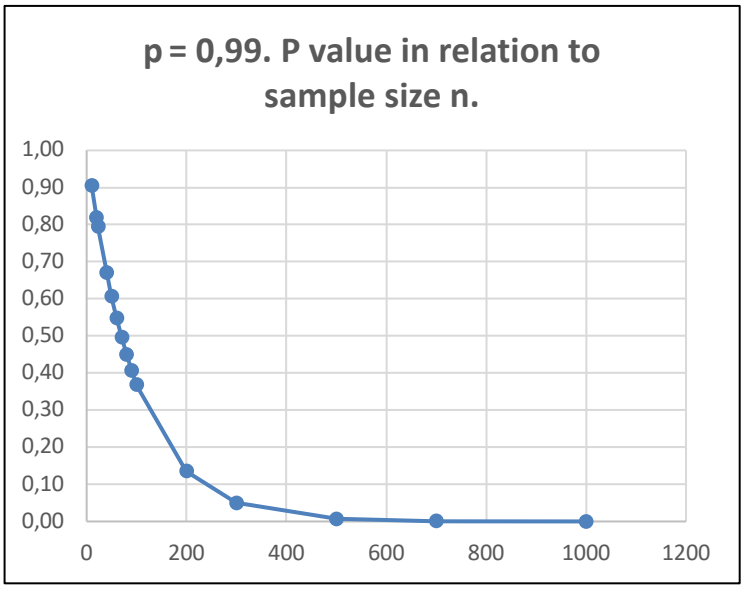

Figure 3. Distribution function

In other words, the (*left* tailed) one-sided null and alternative hypotheses are

$$\begin{aligned} H_0: \quad & \pi(population) \quad \leq \quad p(sample\ proportion) \quad (i.e.\ SINE\ relationship: \text{NO}) \\ H_A: \quad & \pi(population) \quad > \quad p(sample\ proportion) \quad (i.e.\ SINE\ relationship: \text{YES}) \end{aligned} \tag{66}$$

while the *probability* can be calculated as

$$p(X \leq \text{n} - 1) \quad + \quad p(X > \text{n} - 1) \quad \equiv \quad 1 \tag{67}$$

Mathematically, if **X > n-1** then it is **X = n**. The equation before changes to

$$p(X \leq \text{n} - 1) \quad + \quad p(X = \text{n}) \quad \equiv \quad 1 \tag{68}$$

and at the end to

$$p(X \leq \text{n} - 1) \quad \equiv \quad \sum_{t=+0}^{n-1} p(X = t) \quad \equiv \quad 1 \quad - \quad p(X = \text{n}) \tag{69}$$

Thus far, we obtain

$$p(X \leq \text{n} - 1) \quad \equiv \quad \left(\left(\frac{E(\underline{X}\ )}{E(X\ )} \right) \times \left(e^{-\frac{E(\underline{X}\ )}{n}} \right) \right) \tag{70}$$

as the left-tailed P Value for likely events. A *P value* which is less than a chosen significance level α (**P value < α**), suggests that the observed data are potentially inconsistent with the null hypothesis (π(population) ≤ p(sample proportion)) and implicate the conclusion that the null hypothesis should be rejected and we do accept the alternative hypothesis which claims that π(population) > p(sample proportion). If the *P value* is greater than or equal to the significance level α (**P value ≥ α**), we fail to reject the null hypothesis. Under these circumstance it is necessary to accept that the null-hypothesis: π(population) ≤ p(sample proportion).

Example.

To hypothesis test with the distribution before, we must calculate the probability, p, of the observed event and any more extreme event happening. We compare this degree of evidence to the level of significance α. Thus far, if the calculate p is $p > \alpha$ then we do accept the null hypothesis and reject the alternative hypothesis. Under circumstances where $p < \alpha$ we do reject the null hypothesis and accept the alternative hypothesis. The *(left tailed) one-sided* null and alternative hypotheses may be as follows:

$$\begin{aligned} H_0: \quad \pi \quad &\leq \quad p(sample\ proportion) \quad (i.e.\ SINE\ relationship: \text{NO}) \\ H_A: \quad \pi \quad &> \quad p(sample\ proportion) \quad (i.e.\ SINE\ relationship: \text{YES}) \end{aligned} \tag{71}$$

Lövheim et al. (Lövheim, Gilthorpe, Adolfsson, et al., 2015) investigated the link between herpes simplex virus (HSV-1) type 1 and the development of Alzheimer's disease (AD). The study of Lövheim et al. included *n=3432* persons, the mean follow-up time was 11.3 years. Lövheim et al. analyzed serum samples for anti-HSV antibodies while the incident AD cases were 245. The conditio sine qua non relationship was not found in $E(\underline{X}_t)=14$ out of 3432 cases while the conditio sine qua non relationship was given in $E(X_t) = 3418$ cases. The study of Lövheim et al. (Lövheim, Gilthorpe, Adolfsson, et al., 2015) provided a value of the sample proportion of *the conditio sine qua non relationship* as $p_{Sample}(A_t \leftarrow B_t) = 0{,}995920746$, The theoretical proportion of the conditio sine qua non relationship in the population is $\boldsymbol{\pi(x_t) = 1}$ and demands that X = n and can be calculated in general as

$$p(X = n) \quad = \quad \pi(x_t)^n \quad = \quad \underbrace{1 \times 1 \times \ldots \times 1}_{n\ times} \quad = \quad 1^n \quad = \quad 1 \tag{72}$$

The same value can be calculated due to sample data as

$$p(X = n) \quad = \quad \pi(x_t) \quad = \quad +1 \quad - \quad \left(\frac{E(\underline{X}_t)}{E(X_t)}\right) \times \left(e^{-\frac{E(X_t)}{n}}\right) \quad = 1 - \left(\left(\frac{14}{3414}\right) \times \left(e^{-\frac{14}{3432}}\right)\right) \quad = \quad +0{,}995920712 \tag{73}$$

However, as proofed before, if the probability p(X = n) is equal to p(X = n) = 1- 0,995920712 then the left-tailed P value follows as **P value** = p(X ≤ n-1) = 1- p(X = n) = 1- 0,995920712 = **0,004079288**. The null hypothesis must be rejected (P Value = 0,004079288). According to the data of Lövheim et al. (Lövheim, Gilthorpe, Adolfsson, et al., 2015) **Herpes simplex type 1 is a necessary condition of Alzheimer's disease (P Value = 0,004079288).** In other words, **without** a herpes simplex type 1 infection **no** Alzheimer's disease. The conditio sine qua non relationship between HSV-1 and AD is not given only in about 4 out of 1000 cases.

Under some assumptions, the equation above is just a special case of the exponential distribution. In this context let us define the following. Let

$$\lambda \quad \equiv \quad \left(\frac{E(\underline{X}\ )}{E(X\ )}\right) \quad and \quad p \equiv \quad \frac{E(X\ )}{n} \tag{74}$$

while λ is the parameter of the distribution, often called *the rate parameter*. From this follows that

$$E(\underline{X}\ ) \quad = \quad \lambda \times E(X\ ) \tag{75}$$

Substituting these relationships into the equation above it is

$$1 - \pi(x_t) \quad = \quad \left(\frac{E(\underline{X}\ )}{E(X\ )}\right) \times \left(e^{-\frac{E(\underline{X}\ )}{n}}\right) \quad = \quad \lambda \times \left(e^{-\frac{\lambda \times E(X\ )}{n}}\right) \tag{76}$$

The probability density function (pdf) of an exponential distribution follows as

$$1 - \pi(x_t) \quad = \quad \left(\frac{E(\underline{X}\ )}{E(X\ )}\right) \times \left(e^{-\frac{E(\underline{X}\ )}{n}}\right) \quad = \quad \lambda \times \left(e^{-\lambda \times p}\right) \tag{77}$$

Definition 14. The critical value of the necessary condition

Under certain conditions (I. Barukčić, 2019c), the critical P value i. e. of *the conditio sine qua non relationship* $p_{Critical}$ can be calculated as

$$p_{Critical}(A_t \leftarrow B_t\ ) \quad \equiv \quad e^{-\ Alpha} \tag{78}$$

where *Alpha* denotes the level of significance i. e. Alpha = 0,05 and *e* denotes Euler's number (Euler, 1736), the base of the natural logarithm. *The rule of three* (Hanley, 1983; Jovanovic & Levy, 1997; Louis, 1981; Rumke, 1975), defined as

$$p_{Critical}(A_t \leftarrow B_t) \equiv 1 - \left(\frac{3}{n}\right) \tag{79}$$

where *n* denotes the sample size is another way to calculate approximately the critical value for $n > 50$ (Sachs, 1992). In this context, interval estimation of binomial proportions is one of the most basic problems in statistics. The Wald interval is more or less the standard interval for the binomial proportion. The Wald method itself is based on the asymptotically normal approximation to the distribution of the observed sample proportion. However, the standard *Wald interval* has a very poor performance (Agresti & Coull, 1998; DasGupta, Cai, & Brown, 2001), even for a very large sample size. Even an 'exact' confidence interval for the binomial proportion as proposed by Clopper & Pearson 1934 (Clopper & Pearson, 1934) are of a restricted (Blyth & Still, 1983) value due to the very wide interval length. In the following we will demonstrate how the population proportion of *the conditio sine qua non relationship* with some limits can be estimated through the usage of a confidence interval known as a *one-sample proportion* in the Z-interval. Let Z denote the critical value of the standard normal distribution for a level of confidence C = 0,95. Thus far, it is

$$Z\ (A_t \leftarrow B_t) \equiv \frac{1-C}{2} \equiv \frac{1-0{,}95}{2} = 0{,}025 \tag{80}$$

The value for Z of a standard normal bell curve gives an upper tail area of 0.0250 or an area of 1 - 0.0250 = 0.9750. Thus far, for α = 0,05 the (1–(α/2)) quantile of a standard normal distribution is (1– (0,05/2)) or equal to Z = 1,959963985. Hence, based on the formula for the one-sample proportion in the Z-interval, the *upper* critical value of a (1- α) confidence interval of the sample proportion without continuity correction can be calculated according to Wald's method (Wald, 1943) as

$$p_{Upper}(A_t \leftarrow B_t) \equiv p_{Sample}(A_t \leftarrow B_t) + \left(\sqrt[2]{\frac{\left(Z^2_{(\alpha/2)}\right) \times \left(p_{Sample}\right) \times \left(1 - p_{Sample}\right)}{n}}\right) \tag{81}$$

where *n* denotes the sample size, $p_{Sample}(A_t \leftarrow B_t)$ denotes the sample proportion of *the conditio sine qua non relationship* determined by the number of successes in *n* Bernoulli trials, Z is the (1–(α/2)) quantile of a standard normal distribution and α is the level of significance. The lower confidence bound can be calculated as

$$p_{Lower}(A_t \leftarrow B_t) \equiv p_{Sample}(A_t \leftarrow B_t) - \left(\sqrt[2]{\frac{\left(Z^2_{(\alpha/2)}\right) \times \left(p_{Sample}(A_t \leftarrow B_t)\right) \times \left(1 - p_{Sample}(A_t \leftarrow B_t)\right)}{n}}\right) \tag{82}$$

In general, the maximum value is $(p_{Sample}(A_t \leftarrow B_t) \times (1 - p_{Sample}(A_t \leftarrow B_t))) \leq (1/4)$. Let $Z^2 = 4$, and let $\mathbf{p_{Sample}(A_t \leftarrow B_t) = 1}$. A more simple and robust form of the equation before simplifies in contrast to Barukčić (I. Barukčić, 2018c) as

$$p_{Lower}(A_t \leftarrow B_t) \equiv 1 - \left(\sqrt[2]{\frac{(4) \times \left(\frac{1}{4}\right)}{n}}\right) \equiv 1 - \left(\sqrt[2]{\frac{1}{n}}\right) \tag{83}$$

and provides an approximate value. The study of Lövheim et al. (Lövheim, Gilthorpe, Adolfsson, et al., 2015) has an value of the sample proportion of *the conditio sine qua non relationship* $\mathbf{p_{Sample}(A_t \leftarrow B_t) = 0{,}995920746}$, while the approximate lower bound can be calculated as $\mathbf{p_{Lower} = 0{,}982930281}$. A distribution of sample means even if same is drawn from a non-normal distribution follows under some circumstances more or less the normal distribution. In this context, the z-score is defined as

$$Z(A_t \leftarrow B_t) \equiv \frac{\left(X(A_t \leftarrow B_t) - \left(E(A_t \leftarrow B_t)\right)\right)}{\sigma(A_t \leftarrow B_t)} \tag{84}$$

where $E(A_t \leftarrow B_t)$ is the mean or the expected value of the population and σ is the standard deviation of the population. Under circumstances where the population mean and the population standard deviation are unknown,

the standard score Z may be calculated while using the sample mean and sample standard deviation as estimates of the population values.

CLAIM.

The value of *the proportion of an event within the population* denoted as $\pi(x_t)$ can be calculated approximately from the number of missed successes in *n* trials $E(\underline{X}_t) = n - E(X_t) = 0, 1, 2, ..., n$ by the function:

$$\pi(x_t) = +1 - \frac{(\underline{X})^2}{Z(x_t)^2 \times n} \tag{85}$$

PROOF.

In general, it is

$$\pi(x_t) = \pi(x_t) \tag{86}$$

or equally

$$\pi(x_t) = \pi(x_t) + 0 \tag{87}$$

or equally

$$\pi(x_t) = \pi(x_t) + 1 - 1 \tag{88}$$

or equally

$$\pi(x_t) = +1 - (1 - \pi(x_t)) \tag{89}$$

Rearranging equation, it is

$$\pi(x_t) = +1 - \frac{(1 - \pi(x_t)) \times \boldsymbol{n} \times \boldsymbol{\pi(x_t)}}{\boldsymbol{n} \times \boldsymbol{\pi(x_t)}} \tag{90}$$

A binomial random variable regarded; *the variance* is $\sigma(x_t)^2 = n \times \pi(x_t) \times (1 - \pi(x_t))$ while *the expectation value* $E(x_t)$ is defined as $E(x_t) = n \times \pi(x_t)$. The equation before simplifies as

$$\pi(x_t) = +1 - \frac{\boldsymbol{\sigma(x_t)^2}}{\boldsymbol{E(x_t)}} \tag{91}$$

From the definition of the z score, we obtain

$$\sigma(A_t \leftarrow B_t)^2 \equiv \frac{\left(X - \left(E(x_t)\right)\right)^2}{Z(x_t)^2} \tag{92}$$

The equation before can be rearranged as

$$\pi(x_t) = +1 - \frac{\left(\boldsymbol{X} - \left(\boldsymbol{E(x_t)}\right)\right)^2}{\boldsymbol{Z(x_t)^2} \times E(x_t)} \tag{93}$$

Under conditions where the expectation value is $E(x_t) = n \times \pi(x_t) = n \times 1 = n$, the equation before simplifies as

$$\pi(x_t) = +1 - \frac{(X - n)^2}{Z(x_t)^2 \times n} \tag{94}$$

Let $\underline{X} = N - X$ denote the number of failures in *n* Bernoulli trials. The value of *the proportion of an event within the population* denoted as $\pi(x_t)$ follows approximately for values $\underline{X}^2 < Z(x_t)^2 \times n$ as

$$\pi(x_t) = +1 - \frac{(\underline{X})^2}{Z(x_t)^2 \times n} \tag{95}$$

while $Z(x_t)$ is the known Z score.

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Example.

Using the data of Lövheim et al. (Lövheim, Gilthorpe, Adolfsson, et al., 2015) it is to be considered that $\underline{X} = 14$ cases. The population proportion for a z score z = 3,5 follows approximately as

$$\pi(x_t) = +1 - \frac{14 \times 14}{3{,}5 \times 3{,}5 \times 3432} = 0{,}99533800 \quad (96)$$

The probability value associated with Z=3,5 is *0,000232629*. The sample proportion calculated was *0,995920746*.

CLAIM.

The *proportion of an event within the population* denoted as $\pi(x_t)$ can be calculated approximately from the number of missed successes in *n* trials $E(\underline{X}_t) = n - E(X_t) = 0, 1, 2, ..., n$ by the function:

$$\pi(x_t) = +1 - \frac{\chi^2(x_t)}{E(\underline{X})} \quad (97)$$

PROOF.

In general, we expect that the observed value of the probability or of the sample proportion $p(x_t)$ of a binomial distributed random variable is not significantly different from the expected value of the probability or of the population proportion of a binomial distributed random variable in the population, $\pi(x_t)$. In other words, it is

$$\pi(x_t) = \pi(x_t) \quad (98)$$

or equally

$$\pi(x_t) = \pi(x_t) + 0 \quad (99)$$

or equally

$$\pi(x_t) = \pi(x_t) + 1 - 1 \quad (100)$$

or equally

$$\pi(x_t) = +1 - \left(1 - \pi(x_t)\right) \quad (101)$$

Rearranging equation, it is

$$\pi(x_t) = +1 - \frac{\left(1 - \pi(x_t)\right) \times \left(\mathbf{1} - \boldsymbol{\pi}(\boldsymbol{x_t})\right) \times \boldsymbol{n} \times \boldsymbol{n}}{\left(\mathbf{1} - \boldsymbol{\pi}(\boldsymbol{x_t})\right) \times \boldsymbol{n} \times \boldsymbol{n}} \quad (102)$$

The sample proportion $p(x_t)=(X_t/n)$ is the number of successes X_t over the number of trials n. The expected value $E(p(x_t))$ of the sample proportion is an unbiased estimator of the population proportion $\pi(x_t)$. The variance $\sigma(X_t/n)^2$ of the sample proportion $p(x_t) = X_t/n$ is equal to the variance of X_t divided by n^2, or $\sigma(X_t/n)^2 = (n \times p(x_t) \times (1-p(x_t)))/n^2$ or $\sigma(X_t/n)^2 = (p(x_t) \times (1-p(x_t)))/n$. Thus far, while the size of the sample *n* increases, the variance of the sample proportion $\sigma(X_t/n)^2$ decreases. The value of the Chi-Square of goodness fit test is defined as

$$\chi^2(x_t) = \frac{\left(n \times \left(1 - \pi(x_t)\right)\right)^2}{n} = \frac{n \times \left(1 - E\left(p(x_t)\right)\right) \times n \times \left(1 - E\left(p(x_t)\right)\right)}{n} \quad (103)$$

Substituting into the equation before, we obtain

$$\pi(x_t) = +1 - \frac{\boldsymbol{\chi^2(x_t)}}{\left(\mathbf{1} - \boldsymbol{\pi}(\boldsymbol{x_t})\right) \times \boldsymbol{n}} \quad (104)$$

Let $E(\underline{X}) = n \times (1-E(p(x_t)))$, it is

$$\pi(x_t) = +1 - \frac{\boldsymbol{\chi^2(x_t)}}{\boldsymbol{E(\underline{X})}} \quad (105)$$

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Under these assumptions, the Chi-square follows as

$$\boldsymbol{\chi^2(x_t)} = \left(1 - \pi(x_t)\right) \times E(\underline{X}) \quad (106)$$

The critical value of the conditio sine qua non relationship can be estimated by *the rule of three* (Hanley, 1983; Jovanovic & Levy, 1997; Louis, 1981; Rumke, 1975) too.

Example.

Using the data of Lövheim et al. (Lövheim, Gilthorpe, Adolfsson, et al., 2015) it is to be considered that $E(x_t) = n \times p(x_t) = 3432\text{-}14 = 3418$ cases. The value of the chi square distribution at alpha = 0,045500264 is equal to $X^2 = 4$. The probability in the population can be estimated approximately ($X^2 = 4$) as

$$\pi(x_t) = +1 - \frac{4}{14} = 0{,}99882972 \tag{107}$$

Definition 15. (The law of large numbers)

Performing the same experiment under the same conditions a large number of times should yield a sample proportion p(x) very close to the population proportion or expected value π(x). As the number of identically distributed, randomly generated variables increases (sample size *n* grows), sample proportion p(x) gets closer to the proportion π(x) of the whole population. In the 16th century, Italian mathematician Gerolamo Cardano (1501–1576) recognized (Cardano, 1545) the Law of Large Numbers but did not provide a mathematical method to prove the same. The sample proportion will tend to become closer to the population proportion as more trials are performed. Jacob Bernoulli (Bernoulli, 1713) provided in his book *Ars Conjectandi* in 1713 a mathematical proof of the law of large numbers (LLN) for a binary random variables. Later, other mathematicians including Chebyshev (Tschébychef, 1846) contributed a more general version of the law of large numbers for averages. *Pafnuty Lvovich Chebyshev* (1821 – 1894) is known for an inequality (Tchébychef, 1867) too, primary (Bienaymé, 1853) published by *Irénée-Jules Bienaymé* (1796-1878) in 1853, which states that

$$p(|1 - p(x)| \geq c) \leq \frac{\sigma(x)^2}{c^2} = \frac{p(x) \times \left(1 - p(x)\right)}{n \times c^2} \tag{108}$$

where p(x) denotes the sample proportion and *n* is the sample size while c is the difference assumed. The P value can be calculated according to the Chebyshev inequality before. Another possible approach to the calculation of the P value is the following. Let x_t denote a Bernoulli distributed random variable with probability $\pi(x_t)$ *while* $\pi(x_t) = 1 - q(x_t)$. Let $E(X) = n \times \pi(x_t)$ denote the number of successes in a sequence of *n* independent Bernoulli experiments. Furthermore, let $E(\underline{X}) = n \times (1 - \pi(x_t)) = n \times q(x_t)$ denote the number of failures or no or false or +0 et cetera in a sequence of *n* independent Bernoulli experiments. Under these conditions it is valid that $E(X_t) + E(\underline{X}_t) = n$. However, as proofed before, a more precise method to calculate the *proportion of an event* is given by the function:

$$\pi(x_t) = e^{-\left(\frac{E(\underline{X})}{n}\right)} \tag{109}$$

The formula before is valid even for the *conditio sine qua non relationship* where $\pi(x_t)$ is expected to be $\pi(x_t) = 1$. In this case, it is equally X = n. Thus far, the exact probability that a random variable X with mean μ=n is less than or equal to *n-1* is given by the formula

$$p(X \leq n - 1) = 1 - \left(e^{-\frac{E(\underline{X})}{\mu}}\right) = 1 - \left(e^{-\frac{E(\underline{X})}{n}}\right) \tag{110}$$

Example.

The P value of the conditio sine qua non relationship between HSV-1 and AD based on the data published by the study of Letenneur et al., 2008 (Letenneur et al., 2008) can be calculated as

$$p(X \leq n - 1) = 1 - \left(e^{-\frac{E(\underline{X}_t)}{\mu}}\right) = 1 - \left(e^{-\frac{8}{490}}\right) = 0{,}016193975 \tag{111}$$

In general, it is *p(n successes in n trials) = 1- p(X ≤ n -1)*. Thus far, the observed data of Letenneur et al., 2008 (Letenneur et al., 2008) are more or less potentially inconsistent with the left tailed null hypothesis that **π(population proportion) ≤ p(sample proportion)** and implicate the conclusion that the null hypothesis should be rejected because the *P value* = 0,016193975 and less than a chosen significance level α (**P value < α**). We do accept the alternative hypothesis that π(population proportion) > p(sample proportion); P value 0,016193975.

However, a *P value* which is greater than or equal then a significance level α (**P value ≥ α**), would provide some preliminary support for the null hypothesis. In point of fact, according to the data of Letenneur et al., 2008 (Letenneur et al., 2008), **without** Herpes simplex type 1 infection **no** Alzheimer's disease (P value = 0,016193975). Herpes simplex type 1 infection is a necessary condition of Alzheimer's disease.

Definition 16. Exclusion (A_t Excludes B_t and Vice Versa Relationship)

The mathematical formula of the *exclusion* (I. Barukčić, 2018d, 1989, 1997, 2017, 2018a, 2018b, 2019d; K. Barukčić & Barukčić, 2016, 2016) relationship (A_t excludes B_t and vice versa) of a population is defined (I. Barukčić, 2019a, 2019d) as

$$\begin{aligned} p(A_t \mid B_t) &\equiv \frac{(b_t) + (c_t) + (d_t)}{N_t} = 1 \\ &\equiv p(b_t) + p(c_t) + p(d_t) \\ &\equiv p(b_t) + p(\underline{A}_t) = p(b_t) + \left(1 - p(A_t)\right) \\ &\equiv p(c_t) + p(\underline{B}_t) = p(c_t) + \left(1 - p(B_t)\right) \\ &\equiv +1. \end{aligned} \tag{112}$$

and used to prove the hypothesis: A_t *excludes* B_t and vice versa. Under which conditions does A_t exclude B_t and vice versa and what are the consequences? The relationship A_t excludes B_t and vice versa is of outstanding importance especially in human medicine because the same relationship allows researchers to identify among other an *antidote against a certain factor*.

Definition 17. The X^2 Test of Goodness of Fit of the Exclusion Relationship

The chi square value with degree of freedom 2-1=1of the exclusion relationship with a *continuity correction* can be calculated (I. Barukčić, 2019a, 2019d) as

$$X^2\left((A \mid B)\mid A\right) \equiv \frac{\left((a) - (1/2)\right)^2}{A} + 0 = 0 \tag{113}$$

Another equivalent method to calculate the chi-square value of a *conditio sine qua non* distribution is defined (I. Barukčić, 2019a, 2019d) as

$$X^2\left((A \mid B)\mid B\right) \equiv \frac{\left((a) - (1/2)\right)^2}{B} + 0 = 0 \tag{114}$$

In particular, the chi square Goodness of Fit Test of the exclusion relationship provides evidence how well observed data compare with the expected theoretical distribution of an exclusion relationship (I. Barukčić, 2019a, 2019d).

Definition 18. Independence

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

$$p(A_t \cap B_t) \equiv p(A_t) \times p(B_t) \tag{115}$$

Definition 19. The Mathematical Formula of the Causal Relationship k (I. Barukčić, 2016a, 2018b, 2018a, 2019d; K. Barukčić & Barukčić, 2016; K. Barukčić, Barukčić, & Barukčić, 2018) is defined *at every single event, at every single Bernoulli trial t,* as

$$k(A_t, B_t) \equiv \frac{p(A_t \cap B_t) - \left(p(A_t) \times p(B_t)\right)}{\sqrt[2]{p(A_t) \times \left(1 - p(A_t)\right) \times p(B_t) \times \left(1 - p(B_t)\right)}} \tag{116}$$

where A_t denotes the cause and B_t denotes the effect. The significance of causal relationship k can be tested by several methods. Under some certain circumstances, the chi-square distribution can be applied too. However, it is necessary to point out again that the mathematical formula of the causal relationship k has nothing to do *neither* with Pearson's concept of correlation *nor* with Pearson's concept of ϕ. Pearson's correlation methods are not identical with causation or correlation and causation must be distinguished, this has been proved (Sober, 2001) many times by different publications.

Definition 20. The 95% Confidence Interval of the Causal Relationship k

The approximate 95% interval for the causal relationship k can be estimated by the formula

$$\left\{k\left(A_t, B_t\right) - \sqrt[2]{\frac{5}{n}} \quad ; \quad k\left(A_t, B_t\right) + \sqrt[2]{\frac{5}{n}}\right\} \tag{117}$$

Definition 21. The Chi Square Distribution

The upper-tail critical values of chi-square distribution (Karl Pearson, 1900) with ν degrees of freedom df = 1 are visualized by **Table .** The P value denotes the probability of exceeding the critical value.

Table 9. The upper-tail critical values of chi-square distribution

(degrees of freedom: 1)

	P value	**Upper tail X^2**
	0.1000000000	2.705543454
	0,083264517	**3**
	0.0500000000	**3.841458821**
	0,045500264	**4**
	0.0400000000	4.217884588
	0.0300000000	4.709292247
	0,025347319	5
	0.0200000000	5.411894431
The chi square distribution	0,014305878	6
	0.0100000000	6.634896601
	0,008150972	7
	0.0010000000	10.82756617
	0.0001000000	15.13670523
	0.0000100000	19.51142096
	0.0000010000	23.92812698
	0.0000001000	28.37398736
	0.0000000100	32.84125335
	0.0000000010	37.32489311
	0.0000000001	41.82145620

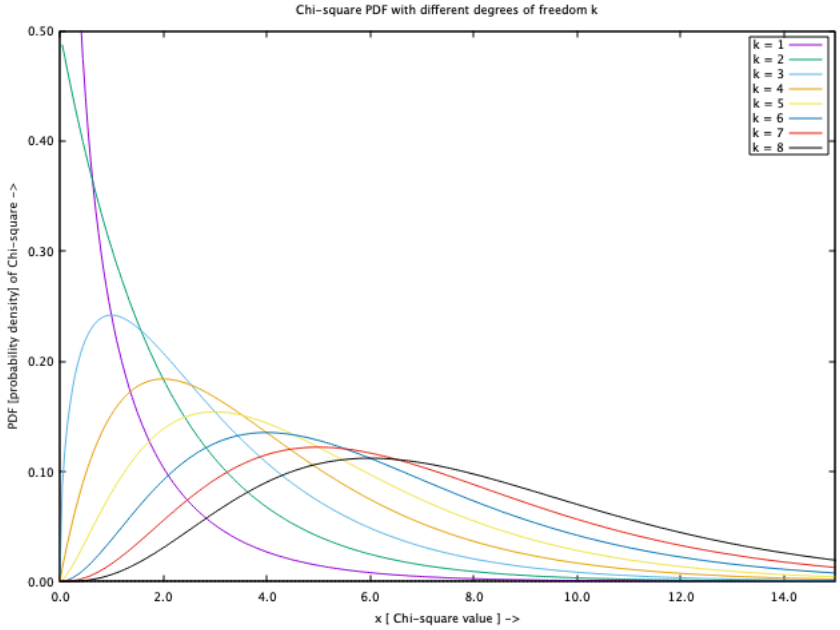

Figure 4. Chi-Square distribution with different degrees of freedom k.

2.2.2. Data analysis

The causal relationship k (I. Barukčić, 1989, 1997, 2016a, 2016b, 2017, 2018a, 2019d; K. Barukčić & Barukčić, 2016; Hessen, 1928; Korch, 1965) was used to proof the data for a causal relationship while the significance was tested by the hypergeometric distribution (HGD) and the chi-square distribution (Karl Pearson, 1900). The *conditio sine qua non* (I. Barukčić, 2018d, 1989, 1997, 2017, 2018a, 2018b, 2019d; K. Barukčić & Barukčić, 2016, 2016) relationship (SINE) was used to proof the hypothesis, *without* HSV-1 infection *no* AD. The *conditio per quam* (I. Barukčić, 2018d, 1989, 1997, 2017, 2018a, 2018b, 2019d; K. Barukčić & Barukčić, 2016, 2016) relationship (IMP) was used to proof the hypothesis, *if* HSV-1 infection *then* AD. The *necessary and sufficient condition* (I. Barukčić, 2018d, 1989, 1997, 2017, 2018a, 2018b, 2019d; K. Barukčić & Barukčić, 2016, 2016) relationship (SINE) was used to proof the hypothesis, (*without* HSV-1 infection *no* AD) **and** (*if* HSV-1 infection *then* AD). The index of unfairness (I. Barukčić, 2019c) was used to control publication bias. All statistical analyses were performed with Microsoft® Excel® for Mac® version 16.2 (181208) software (© 2018, Microsoft GmbH, Munich, Germany). The level of significance was set to 0.05.

3. Results

THEOREM 1. WITHOUT HERPES SIMPLEX TYPE 1 IGG SERO-POSITIVITY NO ALZHEIMER'S DISEASE

CLAIM.

Null-Hypothesis: HSV-1 IgG sero-positivity is a necessary condition of AD.

Alternative Hypothesis: HSV-1 IgG sero-positivity is not a necessary condition of AD.

PROOF.

Several studies considered for meta-analysis (**Table 2**) provided convincing evidence of a conditio sine qua non relationship between HSV-1 and AD. The study of Lövheim et al. (Lövheim, Gilthorpe, Adolfsson, et al., 2015) with a sample size of $n = 3432$ was able to publish data with a sample proportion of $p((HSV - 1) \leftarrow (AD)) = 0{,}996$ of the conditio sine qua non relationship (P Value = 0,004071). At the same time, it was possible to determine the Chi-square values this study as Chi Sq. 1(SINE) = 0,004 and Chi Sq. 2(SINE) = 0,863. Altogether, the studies re-analyzed had a sample size of n = 5053. The studies of Mancuso et al. 2014 with n=134 and of Agostini et al. 2016 with n=120 were considered for meta-analysis too. However, it cannot be excluded that the data of these studies are self-contradictory. The critical Chi-Square value (degrees of freedom = 6, $\alpha = 0{,}05$) of the 6 studies was 12,592. The calculated Chi-Square value was 3,155. In toto, it was not possible to reject the null-hypothesis: **without** a Herpes simplex type 1 IgG positivity **no** Alzheimer's disease. Herpes simplex type 1 IgG positivity is a necessary condition of Alzheimer's disease.

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THEOREM 2. IF HERPES SIMPLEX TYPE 1 PCR DNA POSTMORTEM POSITIVITY THEN ALZHEIMER'S DISEASE

CLAIM.

Null-Hypothesis: HSV-1 PCR DNA postmortem positivity is a sufficient condition of AD.

Alternative Hypothesis: HSV-1 PCR DNA postmortem positivity is not a sufficient condition of AD.

PROOF.

The HSV-1 PCR DNA postmortem studies presented by **Table 5** provided evidence of a sufficient condition relationship between HSV-1 and AD. However, the sample size with n=78 is small. The study of Mori et al. 2004 was analyzed by Fisher's exact test too. Following the post-mortem HSV-1 PCR DNA studies, HSV-1 PCR DNA positivity is a sufficient condition for AD. In other words, **if** HSV-1 PCR DNA postmortem positivity **then** AD.

QUOD ERAT DEMONSTRANDUM.

THEOREM 3. HERPES SIMPLEX TYPE 1 PCR DNA POSTMORTEM POSITIVITY IS A NECESSARY AND SUFFICIENT CONDITION OF AD

CLAIM.

Null-Hypothesis: HSV-1 PCR DNA postmortem positivity is a necessary and sufficient condition of AD.

Alternative-Hypothesis: HSV-1 PCR DNA postmortem positivity is not a necessary and sufficient condition of AD.

PROOF.

The study of Mori et al. 2004 (Mori et al., 2004), analyzed by Fisher's exact test too, provided evidence of a necessary and sufficient condition relationship (**Table 6**) between HSV-1 and AD ($n = 9$; p(necessary and sufficient condition between HSV-1 and AD)= 0,889; Chi Sq. 1(SINE ^IMP) =0,167;Chi Sq. 2(SINE ^IMP) = 0,167). The study design of the study of Mori et al. 2004 was very impressive (p(IOU) + p(IOI) = 0,090909091). Based on HSV-1 PCR DNA postmortem study of Mori et al. 2004, HSV-1 PCR DNA postmortem positivity is a necessary and sufficient condition of AD.

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THEOREM 4. HSV-1 IS THE CAUSE OF AD

CLAIM.

Null-Hypothesis: HSV-1 is not the cause of AD ($k = 0$).

Alternative Hypothesis: HSV-1 is the cause of AD ($k \neq 0$).

PROOF.

The HSV-1 IgG based study of Lövheim et al., 2015 (Lövheim, Gilthorpe, Adolfsson, et al., 2015) provided evidence of a significant cause-effect relationship (Causal relationship k = +0,047; *P value (k | HGD) = 0,00139*; n = 3432; Chi Sq.(k) =7,472; d. f. = 1). The HSV-1 IgG based study of Letenneur et al., 2008 (Letenneur et al., 2008) provided evidence of a significant cause-effect relationship (Causal relationship k = +0,081; *P value (k | HGD) = 0,02574*; n = 490) too. The second HSV-1 IgG based study of Lövheim et al., 2015 (Lövheim, Gilthorpe, Johansson, et al., 2015) provided evidence of a significant cause-effect relationship (causal relationship k = +0,071; P value (k | HGD) = 0,01755). The HSV-1 PCR DNA postmortem based study of Mori et al., 2004 provided evidence of a significant cause-effect relationship between HSV-1 and AD too (causal relationship k = +0,833; P value (k | HGD) = 0,01299). In toto, studies with a sample size of n = 4642 provided evidence of a significant cause-effect relationship between HSV-1 and AD. As demonstrated before, HSV-1 is a necessary condition of AD, HSV-1 is a sufficient condition of AD and HSV-1 is a necessary and sufficient condition of AD. The evidence is overwhelming. **Herpes simplex type 1 is the cause of Alzheimer's disease**.

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4. Discussion

Meanwhile, Dementia is a major global health problem and nearly 35.6 million people live worldwide (WHO, n.d.) with dementia. The prevalence has been reported up to 8% among those aged 65 or more (Tzeng et al., 2018) and the incidence continues to rise (WHO, n.d.). Even if Dementia affects people in all countries, national programmes to address this problem are rarely in place.

In toto, there are several limitations of this study. First of all, not all Patients with probable AD were diagnosed according to the same criteria (McKhann et al., 2011). Furthermore, the laboratory kits used were different and could have impact on quality of the study data. However, the results of *HSV-1 IgG sero-epidemiological studies* which provided evidence of a significant association between HSV-1 and AD cannot be ignored. Even if HSV-1 IgG should not be regarded as the cause of AD, HSV-1 IgG provides an evidence of an HSV-1 infection and is privileged by virtue of being less error prone compared to PCR based studies in this context. Although the study design of the *HSV-1 IgG sero-epidemiological studies* analyzed was more than unfair and less than optimal, these studies where able to document a significant relationship between HSV-1 and AD. In other words, according to the HSV-1 IgG sero-epidemiological studies *without* HSV-1 infection *no* AD. Especially the HSV-1 IgG sero-epidemiological study of Lövheim et al., 2015 (Lövheim, Gilthorpe, Adolfsson, et al., 2015) provided evidence of a significant cause-effect relationship (causal relationship k = +0,047; *P value (k | HGD) =0,00139*; n = 3432; Chi Sq.(k) = 7,472; d. f. = 1) and cannot be ignored. It is worth to mention, that none of the *HSV-1 IgG sero-epidemiological studies* analyzed were able to provide evidence of a sufficient condition relationship between HSV-1 IgG and AD, which is logical too.

Several studies detected HSV-1 DNA in brain tissue from patients with AD and controls (non-neurological cases) using PCR while the study design was far from acceptable. The PCR technology itself can be very faulty (Bacich, Sobek, Cummings, Atwood, & O'Keefe, 2011) and the quality of the results of PCR based investigations depend on several factors (Khot & Fredricks, 2009). Besides of the difficulties due to the PCR method itself, the skill of the investigator, the potential contamination with previously amplified PCR products, the primers used, the quality of the specimen et cetera, the PCR based studies reanalyzed provided striking evidence of the relationship between HSV-1 and AD.

HSV-infected subjects had an almost 3-fold increased risk of developing dementia in comparison to the control group (Tzeng et al., 2018). The usage of anti-herpetic medications in the treatment of HSV infections should be able to reduce the risk of dementia. Tzeng et al. (Tzeng et al., 2018) documented a significant risk reduction of dementia (Ruth F. Itzhaki, 2018b) development in patients affected by HSV infections upon treatment with antiherpetic medications. Patients treated aggressively with antiherpetic medications (Tzeng et al., 2018) had the relative risk of dementia reduced by a factor of 10 (Ruth F. Itzhaki & Lathe, 2018). HSV-1 IgG seropositive

schizophrenia patients treated with *valacyclovir 1.5 g twice daily orally for 18 weeks* compared to HSV-1 IgG seronegative control group improved in working memory, verbal memory, and visual object learning compared with placebo group (Prasad et al., 2013). These and other studies which investigated antiviral drugs acting by different mechanisms (restricting viral replication, blocking viral entry into cells et cetera) support the usage of antiviral drugs for the treatment of AD (Ruth F. Itzhaki, 2016).

The potential usage of antiviral drugs like **acyclovir** (ACV) and **valacyclovir**, the bioactive form of ACV, to treat AD patients, might be most effective especially if combined with other antiviral measures (**intravenous immunoglobulin** (Matthew A. Wozniak & Itzhaki, 2013), **zinc** (Gordon, Asher, & Becker, 1975; Hirano et al., 2008; Kümel, Schrader, Zentgraf, Daus, & Brendel, 1990; Qiu et al., 2013; Shishkov, Varadinova, Panteva, & Bontchev, 1997), **vitamin C** (Lerner et al., 2002; Lerner, Beqaj, Deeter, & Fitzgerald, 2007; Mikirova & Hunninghake, 2014), **lithium** (Skinner, Hartley, Buchan, Harper, & Gallimore, 1980) et cetera). Much work lies ahead for validating the relationship between HSV-1 and AD dementia. Thus far, further research and clinical trials are already ongoing i. e. in Sweden (Lovheim, 2018) and are necessary to explore the underlying mechanism(s) in more detail. In addition, improved hygiene and cleanliness could be useful to prevent the massive spread of Alzheimer's disease too. Viruses like HSV-1 and other too are not only pathogens (Moelling, 2013), **destroyer of human life's** and killers, viruses are **creators of new species**, intelligent designers, building genomes (Koonin, 2016) and major driver of human evolution (Darwin, 1859) too. Viral sequences can be found in the genomes of various organisms to a very great extent. On the long run, an active vaccination against HSV-1 is necessary but should consider several aspects.

5. Conclusion

In summary, the results of this study demand us to accept that *a Herpes simplex type 1 infection is the cause of Alzheimer's disease*.

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Author Contributions

The author confirms being the sole contributor of this work and has approved it for publication.

Conflict of Interest Statement

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. There are no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

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References

Agostini, S., Mancuso, R., Baglio, F., Cabinio, M., Hernis, A., Costa, A. S., … Clerici, M. (2016). High avidity HSV-1 antibodies correlate with absence of amnestic Mild Cognitive Impairment conversion to Alzheimer's disease. *Brain, Behavior, and Immunity*, *58*, 254–260. doi: https://doi.org/10.1016/j.bbi.2016.07.153 [PMID: 27470229]

Agostini, S., Mancuso, R., Baglio, F., Cabinio, M., Hernis, A., Guerini, F. R., … Clerici, M. (2016). Lack of evidence for a role of HHV-6 in the pathogenesis of Alzheimer's disease. *Journal of Alzheimer's Disease: JAD*, *49*(1), 229–235. doi: https://doi.org/10.3233/JAD-150464 [PMID: 26444787]

Agostini, S., Mancuso, R., Hernis, A., Costa, A. S., Nemni, R., & Clerici, M. (2018). HSV-1-Specific IgG Subclasses Distribution and Serum Neutralizing Activity in Alzheimer's Disease and in Mild Cognitive Impairment. *Journal of Alzheimer's Disease: JAD*, *63*(1), 131–138. doi: https://doi.org/10.3233/JAD-170966 [PMID: 29578484]

Agresti, A. (1992). A Survey of Exact Inference for Contingency Tables. *Statistical Science*, *7*(1), 131–153. doi: https://doi.org/10.1214/ss/1177011454

Agresti, A., & Coull, B. A. (1998). Approximate Is Better than "Exact" for Interval Estimation of Binomial Proportions. *The American Statistician*, *52*(2), 119. doi: https://doi.org/10.2307/2685469

Alzheimer, A. (1906). Über einen eigenartigen, schweren Erkrankungsprozeβ der Hirnrinde. *Neurologisches Zentralblatt*, *23*, 1129–1136. Retrieved from https://ci.nii.ac.jp/naid/10030469522/

Alzheimer, A. (1907). Über eine eigenartige Erkrankung der Hirnrinde. *Allgemeine Zeitschrift Fur Psychiatrie Und Psychisch-Gerichtliche Medizin*, *64*, 146–48. Retrieved from https://ci.nii.ac.jp/naid/10030469522/

Arbuthnott, J. (1710). An Argument for Divine Providence, Taken from the Constant Regularity Observ'd in the Births of Both Sexes. By Dr. John Arbuthnott, Physitian in Ordinary to Her Majesty, and Fellow of the College of Physitians and the Royal Society. *Philosophical Transactions of the Royal Society of London*, *27*(325–336), 186–190. doi: https://doi.org/10.1098/rstl.1710.0011

Armstrong, R. (2019). Risk factors for Alzheimer's disease. *Folia Neuropathologica*, *57*(2), 87–105. doi: https://doi.org/10.5114/fn.2019.85929 [PMID: 31556570]

Bacich, D. J., Sobek, K. M., Cummings, J. L., Atwood, A. A., & O'Keefe, D. S. (2011). False negative results from using common PCR reagents. *BMC Research Notes*, *4*, 457. doi: https://doi.org/10.1186/1756-0500-4-457 [PMCID: PMC3219698] [PMID: 22032271]

Ball, M. J. (1982). Limbic predilection in Alzheimer dementia: is reactivated herpesvirus involved? *The Canadian Journal of Neurological Sciences. Le Journal Canadien Des Sciences Neurologiques*, *9*(3), 303–306. doi: https://doi.org/10.1017/s0317167100044115 [PMID: 7116237]

Barnes, L. L., Capuano, A. W., Aiello, A. E., Turner, A. D., Yolken, R. H., Torrey, E. F., & Bennett, D. A. (2015). Cytomegalovirus Infection and Risk of Alzheimer Disease in Older Black and White Individuals. *The Journal of Infectious Diseases*, *211*(2), 230–237. doi: https://doi.org/10.1093/infdis/jiu437 [PMCID: PMC4326304] [PMID: 25108028]

Barukčić, I. (2018d). Human Papillomavirus—The Cause of Human Cervical Cancer. *Journal of Biosciences and Medicines*, *06*(04), 106–125. doi: https://doi.org/10.4236/jbm.2018.64009

Barukčić, I. (1989). *Die Kausalität* (1. Aufl.). Hamburg: Wiss.-Verl.

Barukčić, I. (1997). *Die Kausalität* (2., völlig überarb. Aufl.). Wilhelmshaven: Scientia.

Barukčić, I. (2016a). The Mathematical Formula of the Causal Relationship k. *International Journal of Applied Physics and Mathematics*, *6*(2), 45–65. doi: https://doi.org/10.17706/ijapm.2016.6.2.45-65

Barukčić, I. (2016b). Unified Field Theory. *Journal of Applied Mathematics and Physics*, *04*(08), 1379–1438. doi: https://doi.org/10.4236/jamp.2016.48147

Barukčić, I. (2017). *Die Kausalität* (Reprint of first Edition 1989.). Norderstedt: Books on Demand.

Barukčić, I. (2018a). Epstein-barr virus is the cause of multiple sclerosis. *International Journal of Current Medical and Pharmaceutical Research*, *4*(9 (A)), 3674–3682. doi: https://doi.org/10.24327/23956429.ijcmpr20180538

Barukčić, I. (2018b). Helicobacter Pylori is the Cause of Gastric Cancer. *Modern Health Science*, *1*(1), 43–50. doi: https://doi.org/10.30560/mhs.v1n1p43

Barukčić, I. (2018c). Human Cytomegalovirus is the Cause of Glioblastoma Multiforme. *Modern Health Science*, *1*(2), 19. doi: https://doi.org/10.30560/mhs.v1n2p19

Barukčić, I. (2019a). Human papillomavirus is the cause of human prostate cancer. *Journal of Drug Delivery and Therapeutics*, *9*(4-s), 577–588. doi: https://doi.org/10.22270/jddt.v9i4-s.3385

Barukčić, I. (2019b). Index of Independence. *Modern Health Science*, *2*(2), p1–p1. doi: https://doi.org/10.30560/mhs.v2n2p1

Barukčić, I. (2019c). Index of Unfairness. *Modern Health Science*, *2*(1), p22. doi: https://doi.org/10.30560/mhs.v2n1p22

Barukčić, I. (2019d). Smoking of tobacco is the cause of human lung cancer. *Journal of Drug Delivery and Therapeutics*, *9*(1-s), 148–160. doi: https://doi.org/10.22270/jddt.v9i1-s.2273

Barukčić, K., & Barukčić, I. (2016). Epstein Barr Virus—The Cause of Multiple Sclerosis. *Journal of Applied Mathematics and Physics*, *04*(06), 1042–1053. doi: https://doi.org/10.4236/jamp.2016.46109

Barukčić, K., Barukčić, J. P., & Barukčić, I. (2018). Epstein-Barr virus is the cause of rheumatoid arthritis. *Romanian Journal of Rheumatology*, *27*(4), 148–163. Retrieved from https://view.publitas.com/amph/rjr_2018_4_art-02/page/1

Beffert, U., Bertrand, P., Champagne, D., Gauthier, S., & Poirier, J. (1998). HSV-1 in brain and risk of Alzheimer's disease. *Lancet (London, England)*, *351*(9112), 1330–1331. doi: https://doi.org/10.1016/S0140-6736(05)79057-7 [PMID: 9643802]

Bergh, D. (2015). Chi-Squared Test of Fit and Sample Size-A Comparison between a Random Sample Approach and a Chi-Square Value Adjustment Method. *Journal of Applied Measurement*, *16*(2), 204–217. [PMID: 26075668]

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

Bertolaccini, L., Viti, A., & Terzi, A. (2016). Are the fallacies of the P value finally ended? *Journal of Thoracic Disease*, *8*(6), 1067–1068. doi: https://doi.org/10.21037/jtd.2016.04.48 [PMCID: PMC4885969] [PMID: 27293821]

Bertrand, P. (1993). Distribution of herpes simplex virus type1 DNA in selected areas of normal and Alzheimer's disease brains: a PCR study. *Neurodegeneration*, *2*, 201–218.

Bienaymé, I.-J. (1853). Considérations a l'appui de la découverte de Laplace sur la loi de probabilité dans la méthode des moindres carrés. *Comptes Rendus Des Séances de l'Académie Des Sciences Des Paris*, *37*, 309–324.

Blyth, C. R., & Still, H. A. (1983). Binomial Confidence Intervals. *Journal of the American Statistical Association*, *78*(381), 108–116. doi: https://doi.org/10.1080/01621459.1983.10477938

Bu, X.-L., Yao, X.-Q., Jiao, S.-S., Zeng, F., Liu, Y.-H., Xiang, Y., … Wang, Y.-J. (2015). A study on the association between infectious burden and Alzheimer's disease. *European Journal of Neurology*, *22*(12), 1519–1525. doi: https://doi.org/10.1111/ene.12477 [PMID: 24910016]

Burgos, J. S., Ramirez, C., Sastre, I., Alfaro, J. M., & Valdivieso, F. (2005). Herpes simplex virus type 1 infection via the bloodstream with apolipoprotein E dependence in the gonads is influenced by gender. *Journal of Virology*, *79*(3), 1605–1612. doi: https://doi.org/10.1128/JVI.79.3.1605-1612.2005 [PMCID: PMC544102] [PMID: 15650186]

Cardano, G. (1545). *Artis magnae, sive de regulis algebraicis, liber unus. Qui & totius operis de arithmetica, quod opus perfectum inscripsit, est in ordine decimus*. Nürnberg (Holy Roman Empire): Petreius. doi: https://doi.org/10.3931/e-rara-9159

Cheon, M. S., Bajo, M., Gulesserian, T., Cairns, N., & Lubec, G. (2001). Evidence for the relation of herpes simplex virus type 1 to Down syndrome and Alzheimer's disease. *Electrophoresis*, *22*(3), 445–448. doi: https://doi.org/10.1002/1522-2683(200102)22:3<445::AID-ELPS445>3.0.CO;2-8 [PMID: 11258753]

Clopper, C. J., & Pearson, E. S. (1934). The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. *Biometrika*, *26*(4), 404. doi: https://doi.org/10.2307/2331986

Dahiru, T. (2008). P-value, a true test of statistical significance? A cautionary note. *Annals of Ibadan Postgraduate*

Medicine, *6*(1), 21–26. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4111019/ [PMCID: PMC4111019] [PMID: 25161440]

Darwin, C. (1859). *On the origin of species by means of natural selection, or the preservation of favoured races in the struggle for life*. London (GB): Murray. Retrieved from https://www.e-rara.ch/zut/2309277

DasGupta, A., Cai, T. T., & Brown, L. D. (2001). Interval Estimation for a Binomial Proportion. *Statistical Science*, *16*(2), 101–133. doi: https://doi.org/10.1214/ss/1009213286

De Chiara, G., Marcocci, M. E., Sgarbanti, R., Civitelli, L., Ripoli, C., Piacentini, R., … Palamara, A. T. (2012). Infectious agents and neurodegeneration. *Molecular Neurobiology*, *46*(3), 614–638. doi: https://doi.org/10.1007/s12035-012-8320-7 [PMCID: PMC3496540] [PMID: 22899188]

Deatly, A. M., Haase, A. T., Fewster, P. H., Lewis, E., & Ball, M. J. (1990). Human herpes virus infections and Alzheimer's disease. *Neuropathology and Applied Neurobiology*, *16*(3), 213–223. doi: https://doi.org/10.1111/j.1365-2990.1990.tb01158.x [PMID: 2169597]

DeGroot, M. H., Schervish, M. J., Fang, X., Lu, L., & Li, D. (2005). *Probability and Statistics* (Third Edition [Rep. & arr. ed.]). Beijing (China): Higher Education Press.

Dixon, P. (2003). The p-value fallacy and how to avoid it. *Canadian Journal of Experimental Psychology = Revue Canadienne De Psychologie Experimentale*, *57*(3), 189–202. [PMID: 14596477]

Drouin, E., & Drouin, G. (2017). The first report of Alzheimer's disease. *The Lancet Neurology*, *16*, 687. doi: https://doi.org/10.1016/S1474-4422(17)30258-2

Euler, L. (1736). *Mechanica sive motus scientia analytice exposita*. ex typographia Academiae Scientiarum. doi: https://doi.org/10.3931/e-rara-20558

Féart, C., Helmer, C., Fleury, H., Béjot, Y., Ritchie, K., Amouyel, P., … Dartigues, J.-F. (2011). Association between IgM anti-herpes simplex virus and plasma amyloid-beta levels. *PloS One*, *6*(12), e29480. doi: https://doi.org/10.1371/journal.pone.0029480 [PMCID: PMC3247269] [PMID: 22216291]

Fisher, R. A. (1922). On the Interpretation of $\chi 2$ from Contingency Tables, and the Calculation of P. *Journal of the Royal Statistical Society*, *85*(1), 87–94. doi: https://doi.org/10.2307/2340521

Fisher, Ronald A. (1925). *Statistical Methods for Research Workers*. Edinburgh: Oliver and Boyd. Retrieved from http://www.haghish.com/resources/materials/Statistical_Methods_for_Research_Workers.pdf

Gordon, Y. J., Asher, Y., & Becker, Y. (1975). Irreversible inhibition of herpes simplex virus replication in BSC-1 cells by zinc ions. *Antimicrobial Agents and Chemotherapy*, *8*(3), 377–380. doi: https://doi.org/10.1128/aac.8.3.377 [PMCID: PMC429321] [PMID: 170858]

Hanley, J. A. (1983). If Nothing Goes Wrong, Is Everything All Right? *JAMA*, *249*(13), 1743.

Harris, S. A., & Harris, E. A. (2018). Molecular Mechanisms for Herpes Simplex Virus Type 1 Pathogenesis in Alzheimer's Disease. *Frontiers in Aging Neuroscience*, *10*. doi: https://doi.org/10.3389/fnagi.2018.00048 [PMCID: PMC5845560] [PMID: 29559905]

Hemling, N., Röyttä, M., Rinne, J., Pöllänen, P., Broberg, E., Tapio, V., … Hukkanen, V. (2003). Herpesviruses in brains in Alzheimer's and Parkinson's diseases. *Annals of Neurology*, *54*(2), 267–271. doi: https://doi.org/10.1002/ana.10662 [PMID: 12891684]

Henderson, A. S. (1988). The risk factors for Alzheimer's disease: a review and a hypothesis. *Acta Psychiatrica Scandinavica*, *78*(3), 257–275. doi: https://doi.org/10.1111/j.1600-0447.1988.tb06336.x [PMID: 3057813]

Hessen, J. (1928). *Das Kausalprinzip*. Augsburg: Filser.

Heyde, C. C., & Seneta, E. (Eds.). (2001). *Statisticians of the centuries*. New York: Springer.

Hippius, H., & Neundörfer, G. (2003). The discovery of Alzheimer's disease. *Dialogues in Clinical Neuroscience*, *5*(1), 101–108. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3181715/ [PMCID: PMC3181715] [PMID: 22034141]

Hirano, T., Murakami, M., Fukada, T., Nishida, K., Yamasaki, S., & Suzuki, T. (2008). Roles of zinc and zinc signaling in immunity: zinc as an intracellular signaling molecule. *Advances in Immunology*, *97*, 149–176. doi: https://doi.org/10.1016/S0065-2776(08)00003-5 [PMID: 18501770]

Imtiaz, B., Tolppanen, A.-M., Kivipelto, M., & Soininen, H. (2014). Future directions in Alzheimer's disease from risk factors to prevention. *Biochemical Pharmacology*, *88*(4), 661–670. doi:

https://doi.org/10.1016/j.bcp.2014.01.003 [PMID: 24418410]

Itabashi, S., Arai, H., Matsui, T., Higuchi, S., & Sasaki, H. (1997). Herpes simplex virus and risk of Alzheimer's disease. *Lancet (London, England)*, *349*(9058), 1102. doi: https://doi.org/10.1016/S0140-6736(05)62325-2 [PMID: 9107270]

Itzhaki, R. F., Lin, W. R., Shang, D., Wilcock, G. K., Faragher, B., & Jamieson, G. A. (1997). Herpes simplex virus type 1 in brain and risk of Alzheimer's disease. *Lancet (London, England)*, *349*(9047), 241–244. doi: https://doi.org/10.1016/S0140-6736(96)10149-5 [PMID: 9014911]

Itzhaki, Ruth F. (2016). Herpes and Alzheimer's Disease: Subversion in the Central Nervous System and How It Might Be Halted. *Journal of Alzheimer's Disease: JAD*, *54*(4), 1273–1281. doi: https://doi.org/10.3233/JAD-160607 [PMID: 27497484]

Itzhaki, Ruth F. (2017). Herpes simplex virus type 1 and Alzheimer's disease: possible mechanisms and signposts. *FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology*, *31*(8), 3216–3226. doi: https://doi.org/10.1096/fj.201700360 [PMID: 28765170]

Itzhaki, Ruth F. (2018a). Corroboration of a Major Role for Herpes Simplex Virus Type 1 in Alzheimer's Disease. *Frontiers in Aging Neuroscience*, *10*. doi: https://doi.org/10.3389/fnagi.2018.00324 [PMCID: PMC6202583] [PMID: 30405395]

Itzhaki, Ruth F. (2018b). Corroboration of a Major Role for Herpes Simplex Virus Type 1 in Alzheimer's Disease. *Frontiers in Aging Neuroscience*, *10*, 324. doi: https://doi.org/10.3389/fnagi.2018.00324 [PMCID: PMC6202583] [PMID: 30405395]

Itzhaki, Ruth F., & Lathe, R. (2018). Herpes Viruses and Senile Dementia: First Population Evidence for a Causal Link. *Journal of Alzheimer's Disease: JAD*, *64*(2), 363–366. doi: https://doi.org/10.3233/JAD-180266 [PMID: 29889070]

Jamieson, G. A., Maitland, N. J., Craske, J., Wilcock, G. K., & Itzhaki, R. F. (1991). Detection of herpes simplex virus type 1 DNA sequences in normal and Alzheimer's disease brain using polymerase chain reaction. *Biochemical Society Transactions*, *19*(2), 122S. doi: https://doi.org/10.1042/bst019122s [PMID: 1653719]

Jamieson, G. A., Maitland, N. J., & Itzhaki, R. F. (1992). Herpes simplex virus type 1 DNA sequences are present in aged normal and Alzheimer's disease brain but absent in lymphocytes. *Archives of Gerontology and Geriatrics*, *15 Suppl 1*, 197–201. [PMID: 18647689]

Jamieson, G. A., Maitland, N. J., Wilcock, G. K., Craske, J., & Itzhaki, R. F. (1991). Latent herpes simplex virus type 1 in normal and Alzheimer's disease brains. *Journal of Medical Virology*, *33*(4), 224–227. doi: https://doi.org/10.1002/jmv.1890330403 [PMID: 1649907]

Jovanovic, B. D., & Levy, P. S. (1997). A Look at the Rule of Three. *The American Statistician*, *51*(2), 137–139.

Kastrukoff, L., Hamada, T., Schumacher, U., Long, C., Doherty, P. C., & Koprowski, H. (1982). Central nervous system infection and immune response in mice inoculated into the lip with herpes simplex virus type 1. *Journal of Neuroimmunology*, *2*(3–4), 295–305. doi: https://doi.org/10.1016/0165-5728(82)90062-5 [PMID: 6282930]

Khot, P. D., & Fredricks, D. N. (2009). PCR-based diagnosis of human fungal infections. *Expert Review of Anti-Infective Therapy*, *7*(10), 1201–1221. doi: https://doi.org/10.1586/eri.09.104 [PMCID: PMC2845394] [PMID: 19968513]

Kim, J., Basak, J. M., & Holtzman, D. M. (2009). The role of apolipoprotein E in Alzheimer's disease. *Neuron*, *63*(3), 287–303. doi: https://doi.org/10.1016/j.neuron.2009.06.026 [PMCID: PMC3044446] [PMID: 19679070]

Kittur, S. D., Hoh, J. H., Kawas, C. H., Hayward, G. S., Endo, H., & Adler, W. H. (1992). A molecular hybridization study for the presence of Herpes simplex, cytomegalovirus and Epstein-Barr virus in brain and blood of Alzheimer's disease patients. *Archives of Gerontology and Geriatrics*, *15*(1), 35–41. [PMID: 15374379]

Kobayashi, N., Nagata, T., Shinagawa, S., Oka, N., Shimada, K., Shimizu, A., … Kondo, K. (2013). Increase in the IgG avidity index due to herpes simplex virus type 1 reactivation and its relationship with cognitive function in amnestic mild cognitive impairment and Alzheimer's disease. *Biochemical and Biophysical Research Communications*, *430*(3), 907–911. doi: https://doi.org/10.1016/j.bbrc.2012.12.054 [PMID: 23261465]

Kolmogoroff, A. (1933). *Grundbegriffe der Wahrscheinlichkeitsrechnung*. Berlin, Heidelberg: Springer Berlin

Heidelberg. doi: https://doi.org/10.1007/978-3-642-49888-6

Koonin, E. V. (2016). Viruses and mobile elements as drivers of evolutionary transitions. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *371*(1701). doi: https://doi.org/10.1098/rstb.2015.0442 [PMCID: PMC4958936] [PMID: 27431520]

Korch, H. (1965). *Das Problem der Kausalität*. Berlin: Dt. Verlag der Wissenschaften.

Kosik, K. S., Joachim, C. L., & Selkoe, D. J. (1986). Microtubule-associated protein tau (tau) is a major antigenic component of paired helical filaments in Alzheimer disease. *Proceedings of the National Academy of Sciences of the United States of America*, *83*(11), 4044–4048. doi: https://doi.org/10.1073/pnas.83.11.4044 [PMCID: PMC323662] [PMID: 2424016]

Kümel, G., Schrader, S., Zentgraf, H., Daus, H., & Brendel, M. (1990). The mechanism of the antiherpetic activity of zinc sulphate. *The Journal of General Virology*, *71 (Pt 12)*, 2989–2997. doi: https://doi.org/10.1099/0022-1317-71-12-2989 [PMID: 2177090]

LaPlace, Pierre Simon de. (1812). *Théorie analytique des probabilités*. Paris (France): Courcier. doi: https://doi.org/10.3931/e-rara-9457

Lerner, A. M., Beqaj, S. H., Deeter, R. G., Dworkin, H. J., Zervos, M., Chang, C.-H., … O'Neill, W. (2002). A six-month trial of valacyclovir in the Epstein-Barr virus subset of chronic fatigue syndrome: improvement in left ventricular function. *Drugs of Today (Barcelona, Spain: 1998)*, *38*(8), 549–561. [PMID: 12582420]

Lerner, A. M., Beqaj, S. H., Deeter, R. G., & Fitzgerald, J. T. (2007). Valacyclovir treatment in Epstein-Barr virus subset chronic fatigue syndrome: thirty-six months follow-up. *In Vivo (Athens, Greece)*, *21*(5), 707–713. [PMID: 18019402]

Letenneur, L., Pérès, K., Fleury, H., Garrigue, I., Barberger-Gateau, P., Helmer, C., … Dartigues, J.-F. (2008). Seropositivity to herpes simplex virus antibodies and risk of Alzheimer's disease: a population-based cohort study. *PloS One*, *3*(11), e3637. doi: https://doi.org/10.1371/journal.pone.0003637 [PMCID: PMC2572852] [PMID: 18982063]

Lewandowski, G., Zimmerman, M. N., Denk, L. L., Porter, D. D., & Prince, G. A. (2002). Herpes simplex type 1 infects and establishes latency in the brain and trigeminal ganglia during primary infection of the lip in cotton rats and mice. *Archives of Virology*, *147*(1), 167–179. doi: https://doi.org/10.1007/s705-002-8309-9 [PMID: 11855629]

Lin, W. R., Graham, J., MacGowan, S. M., Wilcock, G. K., & Itzhaki, R. F. (1998). Alzheimer's disease, herpes virus in brain, apolipoprotein E4 and herpes labialis. *ALZHEIMERS REPORTS*, *1*(3). Retrieved from https://ora.ox.ac.uk/objects/uuid:4ffca54d-09ac-4b28-8314-405c653bcc3b

Lin, W. R., Shang, D., & Itzhaki, R. F. (1996). Neurotropic viruses and Alzheimer disease. Interaction of herpes simplex type 1 virus and apolipoprotein E in the etiology of the disease. *Molecular and Chemical Neuropathology*, *28*(1–3), 135–141. doi: https://doi.org/10.1007/BF02815215 [PMID: 8871952]

Lin, W.-R., Wozniak, M. A., Wilcock, G. K., & Itzhaki, R. F. (2002). Cytomegalovirus is present in a very high proportion of brains from vascular dementia patients. *Neurobiology of Disease*, *9*(1), 82–87. doi: https://doi.org/10.1006/nbdi.2001.0465 [PMID: 11848687]

Louis, T. A. (1981). Confidence Intervals for a Binomial Parameter after Observing No Successes. *The American Statistician*, *35*(3), 154–154.

Lovheim, H. (2018). Feasibility and Effects of Valaciclovir Treatment in Persons With Early Alzheimer's Disease (VALZ-Pilot). Retrieved September 27, 2019, from https://clinicaltrials.gov/ct2/show/NCT02997982

Lövheim, H., Gilthorpe, J., Adolfsson, R., Nilsson, L.-G., & Elgh, F. (2015). Reactivated herpes simplex infection increases the risk of Alzheimer's disease. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *11*(6), 593–599. doi: https://doi.org/10.1016/j.jalz.2014.04.522 [PMID: 25043910]

Lövheim, H., Gilthorpe, J., Johansson, A., Eriksson, S., Hallmans, G., & Elgh, F. (2015). Herpes simplex infection and the risk of Alzheimer's disease: A nested case-control study. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *11*(6), 587–592. doi: https://doi.org/10.1016/j.jalz.2014.07.157 [PMID: 25304990]

Mancuso, R., Baglio, F., Agostini, S., Agostini, M. C., Laganà, M. M., Hernis, A., … Clerici, M. (2014). Relationship between herpes simplex virus-1-specific antibody titers and cortical brain damage in Alzheimer's disease and amnestic mild cognitive impairment. *Frontiers in Aging Neuroscience*, *6*. doi: https://doi.org/10.3389/fnagi.2014.00285 [PMCID: PMC4197651] [PMID: 25360113]

Mancuso, R., Baglio, F., Cabinio, M., Calabrese, E., Hernis, A., Nemni, R., & Clerici, M. (2014). Titers of herpes simplex virus type 1 antibodies positively correlate with grey matter volumes in Alzheimer's disease. *Journal of Alzheimer's Disease: JAD*, *38*(4), 741–745. doi: https://doi.org/10.3233/JAD-130977 [PMID: 24072067]

Marques, A. R., Straus, S. E., Fahle, G., Weir, S., Csako, G., & Fischer, S. H. (2001). Lack of association between HSV-1 DNA in the brain, Alzheimer's disease and apolipoprotein E4. *Journal of Neurovirology*, *7*(1), 82–83. doi: https://doi.org/10.1080/135502801300069773 [PMID: 11519487]

McHugh, M. L. (2013). The Chi-square test of independence. *Biochemia Medica*, *23*(2), 143–149. doi: https://doi.org/10.11613/BM.2013.018 [PMCID: PMC3900058] [PMID: 23894860]

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Kawas, C. H., … Phelps, C. H. (2011). The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *7*(3), 263–269. doi: https://doi.org/10.1016/j.jalz.2011.03.005 [PMCID: PMC3312024] [PMID: 21514250]

Mikirova, N., & Hunninghake, R. (2014). Effect of high dose vitamin C on Epstein-Barr viral infection. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research*, *20*, 725–732. doi: https://doi.org/10.12659/MSM.890423 [PMCID: PMC4015650] [PMID: 24793092]

Moelling, K. (2013). What contemporary viruses tell us about evolution: a personal view. *Archives of Virology*, *158*(9), 1833–1848. doi: https://doi.org/10.1007/s00705-013-1679-6 [PMCID: PMC3755228] [PMID: 23568292]

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Annals of Internal Medicine*, *151*(4), 264–964. [PMID: 19622511]

Moivre, A. de [1667-1754]. (1718). *The Doctrine of Chances or a Method of Calculating the Probability of Events in Play*. London: printed by W. Pearson for the author. doi: https://doi.org/10.3931/e-rara-10420

Mori, I., Kimura, Y., Naiki, H., Matsubara, R., Takeuchi, T., Yokochi, T., & Nishiyama, Y. (2004). Reactivation of HSV-1 in the brain of patients with familial Alzheimer's disease. *Journal of Medical Virology*, *73*(4), 605–611. doi: https://doi.org/10.1002/jmv.20133 [PMID: 15221907]

Olsson, J., Lövheim, H., Honkala, E., Karhunen, P. J., Elgh, F., & Kok, E. H. (2016). HSV presence in brains of individuals without dementia: the TASTY brain series. *Disease Models & Mechanisms*, *9*(11), 1349–1355. doi: https://doi.org/10.1242/dmm.026674 [PMCID: PMC5117234] [PMID: 27664135]

Ounanian, A., Guilbert, B., Renversez, J. C., Seigneurin, J. M., & Avrameas, S. (1990). Antibodies to viral antigens, xenoantigens, and autoantigens in Alzheimer's disease. *Journal of Clinical Laboratory Analysis*, *4*(5), 367–375. doi: https://doi.org/10.1002/jcla.1860040510 [PMID: 2172499]

Pandey, J. P., Kothera, R. T., Liu, S., Costa, A. S., Mancuso, R., & Agostini, S. (2019). Immunoglobulin Genes and Immunity to HSV1 in Alzheimer's Disease. *Journal of Alzheimer's Disease: JAD*, *70*(3), 917–924. doi: https://doi.org/10.3233/JAD-190265 [PMID: 31306125]

Pearson, K. (1904). *On the theory of contingency and its relation to association and normal correlation*. London: Dulau and Co.

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

Piacentini, R., De Chiara, G., Li Puma, D. D., Ripoli, C., Marcocci, M. E., Garaci, E., … Grassi, C. (2014). HSV-1 and Alzheimer's disease: more than a hypothesis. *Frontiers in Pharmacology*, *5*, 97. doi: https://doi.org/10.3389/fphar.2014.00097 [PMCID: PMC4019841] [PMID: 24847267]

Pisa, D., Alonso, R., Fernández-Fernández, A. M., Rábano, A., & Carrasco, L. (2017). Polymicrobial Infections In Brain Tissue From Alzheimer's Disease Patients. *Scientific Reports*, *7*(1), 5559. doi: https://doi.org/10.1038/s41598-017-05903-y [PMCID: PMC5514053] [PMID: 28717130]

Prasad, K. M., Eack, S. M., Keshavan, M. S., Yolken, R. H., Iyengar, S., & Nimgaonkar, V. L. (2013). Antiherpes virus-specific treatment and cognition in schizophrenia: a test-of-concept randomized double-blind placebo-controlled trial. *Schizophrenia Bulletin*, *39*(4), 857–866. doi: https://doi.org/10.1093/schbul/sbs040 [PMCID: PMC3686443] [PMID: 22446565]

Qiu, M., Chen, Y., Chu, Y., Song, S., Yang, N., Gao, J., & Wu, Z. (2013). Zinc ionophores pyrithione inhibits

herpes simplex virus replication through interfering with proteasome function and NF-κB activation. *Antiviral Research*, *100*(1), 44–53. doi: https://doi.org/10.1016/j.antiviral.2013.07.001 [PMID: 23867132]

Roberts, G. W., Taylor, G. R., Carter, G. I., Johnson, J. A., Bloxham, C., Brown, R., & Crow, T. J. (1986). Herpes simplex virus: a role in the aetiology of Alzheimer's disease? *Journal of Neurology, Neurosurgery, and Psychiatry*, *49*(2), 216. doi: https://doi.org/10.1136/jnnp.49.2.216 [PMCID: PMC1028693] [PMID: 3005513]

Rodriguez, J. D., Royall, D., Daum, L. T., Kagan-Hallet, K., & Chambers, J. P. (2005). Amplification of Herpes simplex type 1 and Human Herpes type 5 viral DNA from formalin-fixed Alzheimer brain tissue. *Neuroscience Letters*, *390*(1), 37–41. doi: https://doi.org/10.1016/j.neulet.2005.07.052 [PMID: 16118038]

Rumke, C. L. (1975). Implications of the Statement: No Side Effects Were Observed. *The New England Journal of Medicine*, *292*(7), 372–373.

Sachs, L. (1992). *Angewandte Statistik*. Berlin, Heidelberg: Springer Berlin Heidelberg.

Schmutzhard, E. (2001). Viral infections of the CNS with special emphasis on herpes simplex infections. *Journal of Neurology*, *248*(6), 469–477. doi: https://doi.org/10.1007/s004150170155 [PMID: 11499636]

Sekizawa, T., & Openshaw, H. (1984). Encephalitis resulting from reactivation of latent herpes simplex virus in mice. *Journal of Virology*, *50*(1), 263–266. [PMCID: PMC255608] [PMID: 6321795]

Shen, J.-H., Huang, K.-Y. A., Chao-Yu, C., Chen, C.-J., Lin, T.-Y., & Huang, Y.-C. (2015). Seroprevalence of Herpes Simplex Virus Type 1 and 2 in Taiwan and Risk Factor Analysis, 2007. *PloS One*, *10*(8), e0134178. doi: https://doi.org/10.1371/journal.pone.0134178 [PMCID: PMC4529201] [PMID: 26252011]

Shishkov, S., Varadinova, T., Panteva, M., & Bontchev, P. (1997). Effect of Complexes of Zinc, Cobalt and Copper With D-Aminosugars on the Replication of Herpes Simplex Virus Type 1 (HSV-1). *Metal-Based Drugs*, *4*(1), 35–38. doi: https://doi.org/10.1155/MBD.1997.35 [PMCID: PMC2365038] [PMID: 18475763]

Skinner, G. R., Hartley, C., Buchan, A., Harper, L., & Gallimore, P. (1980). The effect of lithium chloride on the replication of herpes simplex virus. *Medical Microbiology and Immunology*, *168*(2), 139–148. [PMID: 6256617]

Sober, E. (2001). Venetian Sea Levels, British Bread Prices, and the Principle of the Common Cause. *The British Journal for the Philosophy of Science*, *52*(2), 331–346.

Sokal, R. R., & Rohlf, F. J. (1995). *Biometry: the principles and practice of statistics in biological research* (3rd ed). New York: W.H. Freeman.

Steel, A. J., & Eslick, G. D. (2015). Herpes Viruses Increase the Risk of Alzheimer's Disease: A Meta-Analysis. *Journal of Alzheimer's Disease: JAD*, *47*(2), 351–364. doi: https://doi.org/10.3233/JAD-140822 [PMID: 26401558]

Steiner, I. (2011). Herpes simplex virus encephalitis: new infection or reactivation? *Current Opinion in Neurology*, *24*(3), 268–274. doi: https://doi.org/10.1097/WCO.0b013e328346be6f [PMID: 21483260]

Tchébychef, P. L. (1867). Des valeurs moyennes. *Journal de Mathématiques Pures et Appliquées*, *2*(12), 177–184.

Tschébychef, P. L. (1846). Démonstration élémentaire d'une proposition générale de la théorie des probabilités. *Journal Für Die Reine Und Angewandte Mathematik (Crelles Journal)*, *1846*(33), 259–267. doi: https://doi.org/10.1515/crll.1846.33.259

Tzeng, N.-S., Chung, C.-H., Lin, F.-H., Chiang, C.-P., Yeh, C.-B., Huang, S.-Y., … Chien, W.-C. (2018). Anti-herpetic Medications and Reduced Risk of Dementia in Patients with Herpes Simplex Virus Infections-a Nationwide, Population-Based Cohort Study in Taiwan. *Neurotherapeutics: The Journal of the American Society for Experimental NeuroTherapeutics*, *15*(2), 417–429. doi: https://doi.org/10.1007/s13311-018-0611-x [PMCID: PMC5935641] [PMID: 29488144]

Wald, A. (1943). Tests of statistical hypotheses concerning several parameters when the number of observations is large. *Transactions of the American Mathematical Society*, *54*(3), 426–482. doi: https://doi.org/10.1090/S0002-9947-1943-0012401-3

Warren-Gash, C., Forbes, H. J., Williamson, E., Breuer, J., Hayward, A. C., Mavrodaris, A., … Smeeth, L. (2019). Human herpesvirus infections and dementia or mild cognitive impairment: a systematic review and meta-analysis. *Scientific Reports*, *9*(1), 4743. doi: https://doi.org/10.1038/s41598-019-41218-w [PMCID: PMC6426940] [PMID: 30894595]

WHO, M. centre. (n.d.). Dementia cases set to triple by 2050 but still largely ignored. Retrieved September 27, 2019, from https://www.who.int/mediacentre/news/releases/2012/dementia_20120411/en/

Wozniak, M. A., Mee, A. P., & Itzhaki, R. F. (2009). Herpes simplex virus type 1 DNA is located within Alzheimer's disease amyloid plaques. *The Journal of Pathology*, *217*(1), 131–138. doi: https://doi.org/10.1002/path.2449 [PMID: 18973185]

Wozniak, Matthew A., Frost, A. L., & Itzhaki, R. F. (2009). Alzheimer's disease-specific tau phosphorylation is induced by herpes simplex virus type 1. *Journal of Alzheimer's Disease: JAD*, *16*(2), 341–350. doi: https://doi.org/10.3233/JAD-2009-0963 [PMID: 19221424]

Wozniak, Matthew A., & Itzhaki, R. F. (2013). Intravenous immunoglobulin reduces β amyloid and abnormal tau formation caused by herpes simplex virus type 1. *Journal of Neuroimmunology*, *257*(1–2), 7–12. doi: https://doi.org/10.1016/j.jneuroim.2013.01.005 [PMID: 23385080]

Wozniak, Matthew A., Shipley, S. J., Combrinck, M., Wilcock, G. K., & Itzhaki, R. F. (2005). Productive herpes simplex virus in brain of elderly normal subjects and Alzheimer's disease patients. *Journal of Medical Virology*, *75*(2), 300–306. doi: https://doi.org/10.1002/jmv.20271 [PMID: 15602731]

Yamane, T. (Ed.). (1964). *Statistics. An introductory analysis*. Harper International Edition.

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