International Journal of Current Science Research
www.drbgrpublications.in

Volume: 5; Issue: 10; October-2019; pp 1822-1840. ISSN: 2454-5422

# Epstein Bar virus is the cause of systemic lupus erythematosus

Ilija Barukčić[1]

[1]Internist, Horandstrasse, DE-26441 Jever, Germany
Corresponding Author E-mail: Barukcic@t-online.de

## Abstract

**Objective.** Several studies provided some evidence that Epstein Barr virus (EBV) might play a role in the pathogenesis of systemic lupus erythematosus (SLE). Still, there are conflicting reports too. To determine whether EBV is causally related to SLE a systematic review of available case control studies was performed.

**Methods.** This systematic review and meta-analysis should answer among other questions the following: is there a cause effect relationship between EBV and SLE? The method of the conditio sine qua non relationship was used to proof the hypothesis *without* EBV infection *no* SLE. The mathematical formula of the causal relationship k was used to proof the hypothesis whether there is a cause effect relationship between Epstein-Barr virus and systemic lupus erythematosus. Significance was indicated by a p-value of less than 0.05.

**Results.** The studies analyzed were able to provide convincing evidence that Epstein-Barr virus is a necessary condition (a conditio sine qua non) of systemic lupus erythematosus. Furthermore, the studies analyzed provide impressive evidence of a cause-effect relationship between Epstein-Barr virus and systemic lupus erythematosus.

**Conclusion.** EBV infection is necessary condition of systemic lupus erythematosus and much more than this. Epstein-Barr virus is the cause of systemic lupus erythematosus.

**Keywords**: *Epstein-Bar virus, systemic lupus erythematosus, causal relationship.*

## 1. Introduction

The Systemic lupus erythematosus is a very complex autoimmune systemic diseases without a definite pathogenesis. SLE is characterized by the presence of multiple autoantibodies (Olsen & Karp, 2014), an impaired cell-mediated immunity, an altered T cell function (Labonte et al., 2018) and by polyclonal B cell activation which may effect

almost any organ system. There are worldwide differences in the prevalence (Rees, Doherty, Grainge, Lanyon, & Zhang, 2017) of SLE. In North America about 241/100 000 people suffer from SLE. The term lupus was coined by *Hebernus of Tours* in his *Miracles of St. Martin* in the tenth century (Gordon & Isenberg, 2016). In 1869/1872, the Hungarian born dermatologist *Moriz Kaposi* was the first to describe the systemic nature of lupus in detail (Kaposi, 1872). *Hargraves* et al. described LE cells in 1948 (Hargraves, Richmond, & Morton, 1948). The first trials towards an understanding of the pathogenesis of lupus were published by Morteo (Morteo, Franklin, Mcewen, Phythyon, & Tanner, 1961), Helyer and Howie (Helyer & Howie, 1963) and Leonhardt (Leonhardt, 1964). Diagnostic criteria for systemic lupus erythematosus were first proposed in 1971 by the American College of Rheumatology (A. S. Cohen, Reynolds, & Franklin, 1971). Philip Showalter Hench (1896–1965), awarded with the 1950 Nobel Prize for Medicine and Physiology, the founding father of glucocorticoid treatment of rheumatoid arthritis (Hench, Kendall, Slocumb, & Polley, 1949), was first to suppress some features of SLE by glucocorticoids in 1950. Steinberg et al. conducted the first randomized clinical trial to treat SLE with cyclophosphamide (Steinberg et al., 1971) in 1971. Epstein-Barr virus infects a majority of individuals worldwide and generates multiple antibodies (Olsen & Karp, 2014) in the serum. It is believed that especially Epstein-Barr virus (EBV) contributes to development of SLE. Evans et al. (Evans, Rothfield, & Niederman, 1971) found in 1971 raised antibody titers to Epstein-Barr virus in systemic lupus erythematosus patients. James et al. (James et al., 1997) found Epstein-Barr viral DNA in peripheral blood lymphocytes of all 32 of the lupus patients but only 23 of the 32 matched controls. Finally, the review and meta-analysis of Hanlon et al. (Hanlon, Avenell, Aucott, & Vickers, 2014) and of Li et al. (Li, Zeng, Wu, & Zhou, 2019) provided some evidence of an association between EBV infection and SLE. However, the previous systematic reviews and meta-analysis have failed to establish Epstein-Barr virus as the cause or a cause of systemic lupus erythematosus. The nature of the relationship between an Epstein-Barr Virus infection and SLE, in particular the question of causality, remains to be fully elucidated.

## 2. Material and Methods

Epstein-Barr Virus (Epstein, Achong, & Barr, 1964) is a herpes virus determined by a large double-stranded DNA genome witch itself is enclosed with an icosahedral capsid, including viral capsid antigen (VCA). EBV is able to infect B cells and to establish a latent cycle while persisting for life within the long-lived human memory B-cell

population (Niller, Wolf, & Minarovits, 2008). EBV possesses several immunomodulatory properties (Kanegane, Wakiguchi, Kanegane, Kurashige, & Tosato, 1997), an EBV replication is associated with expression of some lytic cycle genes (Toussirot & Roudier, 2007), including VCA and early antigen (EA). The detection of EBV antibodies specific for EBV viral antigens is indicative of EBV infection (IgM, EA) or EBV reactivation.

## 2.1. Material

### 2.1.1. Search Strategy

For the questions addressed in this paper, the database PubMed was searched for serologically based studies conducted in any country which investigated the relationship between EBV and SLE by EBV antibodies. Those articles were formally considered for a review which provided access to data without a significant data access barrier.

***The Data of the Studies Analyzed***

| **1. Identification of records** | Size | Total |
|---|---|---|
| Records identified by searching in the databases | | |
| PubMed | 438 | |
| Google Scholar | 0 | |
| Web of Science | 0 | |
| Additional records identified from other sources | 2 | 440 |
| **2. Clean-up of search (Screening)** | | |
| Records removed after verifying duplication | 0 | |
| Records excluded by title | 411 | |
| Records excluded due to other reasons | 2 | |
| (Articles outside the inclusion criteria) | | |
| **3. Eligibility** | | |
| Articles evaluated for eligibility | 27 | |
| Articles excluded for various reasons | | |
| - Data were self-contradictory (Table 2) | 11 | |
| - Data access barriers | 0 | |
| **4. Included** | | |
| Articles included in the meta-analysis (Table 1) | | 16 |

**Table 1.**

Flow Diagram of the article selection process. Adopted from PRISMA 2009 (Moher, Liberati, Tetzlaff, & Altman, 2009).

### 2.1.2. Studies considered for re-analysis

The studies of Yokochi et al. (Yokochi, Yanagawa, Kimura, & Mizushima, 1989), Marchini et al. (Marchini, Dolcher, Sabbatini, Klein, & Migliorini, 1994), Tsai et al. (Tsai, Chiang, Kao, & Hsieh, 1995), James (1997) et al. (James et al., 1997), Westgeest et al. (Westgeest, van Loon, van der Logt, van de Putte, & Boerbooms, 1989), Kitagawa et al. (Kitagawa, Iho, Yokochi, & Hoshino, 1988), Lau et al. (Lau, Yuen, Chan, & Wong, 1998), Stratta et al. (Stratta et al., 1999), James (2001) et al. (James et al., 2001), Chen et al. (C.-J. Chen et al., 2005), Parks et al. (Parks et al., 2005), Berkun et al.

(Berkun et al., 2009), Chen et al. (D.-Y. Chen et al., 2010), Draborg et al. (A. H. Draborg et al., 2012), Csuka et al. (Csuka et al., 2013), Han et al. (Han et al., 2018), were not self-contradictory (**Table 2**) and were considered for meta-analysis.

**Table 2. Studies considered for a reanalysis**

| Study ID | Year | N | Case_P | Case_T | Con_P | Con_T | Odds Ratio | OR 95 % CI lower | OR upper | p(SINE) | $X^2$ (SINE) | p Value (SINE) | k | IOU |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Yokochi et al. | 1989 | 25 | 9 | 11 | 2 | 14 | 27,00 | 3,17 | 229,97 | 0,92000 | 0,3636363636 | 0,5465 | 0,6753 | -0,1200 |
| Marchini et al. | 1994 | 60 | 34 | 40 | 15 | 20 | 1,89 | 0,50 | 7,17 | 0,90000 | 0,9000000000 | 0,3428 | 0,1218 | 0,4833 |
| Tsai et al. | 1995 | 36 | 13 | 16 | 15 | 20 | 1,44 | 0,29 | 7,25 | 0,91667 | 0,5625000000 | 0,4533 | 0,0747 | 0,2222 |
| James et al. | 1997 | 270 | 116 | 117 | 107 | 153 | 49,87 | 6,76 | 367,95 | 0,99630 | 0,0085470085 | 0,9263 | 0,3817 | 0,2593 |
| Westgeest et al. | 1998 | 98 | 10 | 14 | 56 | 84 | 1,25 | 0,36 | 4,34 | 0,95918 | 1,1428571429 | 0,2850 | 0,0355 | -0,1837 |
| Kitagawa et al. | 1998 | 131 | 64 | 65 | 52 | 66 | 17,23 | 2,19 | 135,40 | 0,99237 | 0,0153846154 | 0,9013 | 0,3089 | 0,3817 |
| Lau et al. | 1998 | 56 | 27 | 34 | 4 | 22 | 17,36 | 4,43 | 68,01 | 0,87500 | 1,4411764706 | 0,2299 | 0,6015 | 0,1607 |
| Strata et al. | 1999 | 115 | 55 | 60 | 33 | 55 | 7,33 | 2,53 | 21,22 | 0,95652 | 0,4166666667 | 0,5186 | 0,3732 | 0,2870 |
| James et al. | 2001 | 588 | 195 | 196 | 370 | 392 | 11,59 | 1,55 | 86,67 | 0,99830 | 0,0051020408 | 0,9431 | 0,1241 | 0,2942 |
| Chen et al. | 2005 | 72 | 31 | 36 | 30 | 36 | 1,24 | 0,34 | 4,50 | 0,93056 | 0,6944444444 | 0,4047 | 0,0386 | 0,3472 |
| Parks et al. | 2005 | 506 | 220 | 230 | 256 | 276 | 1,72 | 0,79 | 3,75 | 0,98024 | 0,4347826087 | 0,5097 | 0,0611 | 0,3953 |
| Berkun et al. | 2009 | 260 | 114 | 120 | 127 | 140 | 1,94 | 0,72 | 5,29 | 0,97692 | 0,3000000000 | 0,5839 | 0,0821 | 0,3885 |
| Chen et al. | 2010 | 464 | 81 | 94 | 308 | 370 | 1,25 | 0,66 | 2,39 | 0,97198 | 1,7978723404 | 0,1800 | 0,0320 | 0,0409 |
| Draborg et al. | 2012 | 80 | 48 | 60 | 15 | 20 | 1,33 | 0,40 | 4,40 | 0,85000 | 2,4000000000 | 0,1213 | 0,0529 | 0,5375 |
| Csuka et al. | 2012 | 646 | 286 | 301 | 310 | 345 | 2,15 | 1,15 | 4,03 | 0,97678 | 0,7475083056 | 0,3873 | 0,0964 | 0,3885 |
| Han et al. | 2018 | 192 | 104 | 116 | 68 | 76 | 1,02 | 0,40 | 2,62 | 0,93750 | 1,2413793103 | 0,2652 | 0,0029 | 0,5000 |
| **Total** | | 3599 | 1407 | 1510 | 1768 | 2089 | | | | | | | | +0,274 |

| | |
|---|---|
| Alpha = | 0,05 |
| Degrees of freedom = | 16 |
| **$X^2$ CRITICAL (SINE) =** | **26,296** |
| **$X^2$ Calculated (SINE) =** | **12,47** |

### 2.1.2. Studies not considered for re-analysis

The studies of Ngou et al. 1996 (Ngou & Segondy, 1996), Zhang et al. 1999 (Zhang, Li, Liu, & Jiang, 1999), Huggins et al. 2005 (Huggins, Todd, & Powell, 2005), Tazi et al. 2009 (Tazi, Fehri, Elghrari, Ouazzani, & Benchemsi, 2009), US et al. 2011 (Us, Cetin, Kaşifoğlu, Kaşifoğlu, & Akgün, 2011), Essen et al. 2012 (Esen et al., 2012), Broccolo et al. 2013 (Broccolo et al., 2013), Draborg et al. 2014 (Anette Holck Draborg et al., 2014), Draborg et al. 2016 (Anette Holck Draborg et al., 2016), Vista et al. 2017 (Vista et al., 2017), Chougule et al. 2018 (Chougule et al., 2018) provided self-contradictory data. Even if all but the study of Vista et al. 2017 (Vista et al., 2017) support the hypothesis without EBV infection no SLE the data of these studies where not considered for a re-analysis. The same studies provide evidence of a causal relationship k which is $k < 0$. This is a contradiction. Mathematically it is not possible to

obtain a significant conditio sine qua non relationship, while the causal relationship k is k < 0. The data are potentially biased and were not considered (**Table 3**) for an analysis.

**Table 3. Studies not considered for a re-analysis.**

| Study ID | Year | N | Case_P | Case_T | Con_P | Con_T | Odds Ratio | OR 95 % CI | OR upper | p(SINE) | X2 (SINE) | p Value (SINE) | K | IOU |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ngou et al. | 1996 | 83 | 30 | 33 | 50 | 50 | 0,00 | #ZAHL! | #ZAHL! | 0,96386 | **0,2727272727** | 0,6015 | **-0,2384** | 0,3614 |
| Zang et al. | 1999 | 81 | 28 | 36 | 38 | 45 | 0,64 | 0,21 | 1,99 | 0,90123 | **1,7777777778** | 0,1824 | **-0,0853** | 0,2593 |
| Huggins et al. | 2005 | 61 | 26 | 36 | 22 | 25 | 0,35 | 0,09 | 1,45 | 0,83607 | **2,7777777778** | 0,0956 | **-0,1895** | 0,3770 |
| Tazi et al. | 2009 | 88 | 40 | 44 | 42 | 44 | 0,48 | 0,08 | 2,75 | 0,95455 | **0,3636363636** | 0,5465 | **-0,0902** | 0,4318 |
| US et al. | 2011 | 100 | 49 | 50 | 50 | 50 | 0,00 | #ZAHL! | #ZAHL! | 0,99000 | **0,0200000000** | 0,8875 | **-0,1005** | 0,4900 |
| Essen et al. | 2012 | 263 | 184 | 198 | 64 | 65 | 0,21 | 0,03 | 1,59 | 0,94677 | **0,9898989899** | 0,3198 | **-0,1029** | 0,6958 |
| Broccolo et al. | 2013 | 59 | 18 | 21 | 35 | 38 | 0,51 | 0,09 | 2,81 | 0,94915 | **0,4285714286** | 0,5127 | **-0,1012** | 0,2542 |
| Draborg et al. | 2014 | 44 | 19 | 22 | 21 | 22 | 0,30 | 0,03 | 3,15 | 0,93182 | **0,4090909091** | 0,5224 | **-0,1581** | 0,4091 |
| Draborg et al. | 2016 | 54 | 24 | 27 | 26 | 27 | 0,31 | 0,03 | 3,16 | 0,94444 | **0,3333333333** | 0,5637 | **-0,1414** | 0,4259 |
| Chougule et al. | 2017 | 137 | 76 | 87 | 46 | 50 | 0,60 | 0,18 | 2,00 | 0,91971 | **1,3908045977** | 0,2383 | **-0,0716** | 0,5255 |
| Vista et al. | 2017 | 997 | 202 | 233 | 685 | 764 | 0,75 | 0,48 | 1,17 | 0,96891 | 4,1244635193 | 0,0423 | **-0,0400** | 0,1234 |
| Total | | 1967 | 696 | 787 | 1079 | 1180 | | | | | | | | |

### 2.1.3. Studies considered for causal relationship re-analysis

The concept of causality and causal inference is characterized by an increasingly prominent place in the teaching and practice of human medicine, epidemiology and science as such. However, a single and generally accepted approach to causal inference in science is still not in sight. In particular, this publication analyzed the etiopathogenetic relationship between EBV and SLE (**Table 4**) while relying on antibodies against EBV. The EBV antibodies itself are not regarded as a or as the cause of SLE. Human antibodies against EBV represent a prototype of persistent EBV infection of humans characterized by the property of the latency and reactivation.

**Table 4. Studies considered for a causal analysis**

| Study ID | Year | N | Case_P | Case_T | Con_P | Con_T | Odds Ratio | OR 95 % CI lower | OR upper | p(SINE) | $X^2$ (SINE) | p Value (SINE) | k | p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Yokochi et al. | 1989 | 25 | 9 | 11 | 2 | 14 | 27,00 | 3,17 | 229,97 | 0,92000 | 0,3636363636 | 0,5465 | 0,6753 | 0,0011228519 |
| Marchini et al. | 1994 | 60 | 34 | 40 | 15 | 20 | 1,89 | 0,50 | 7,17 | 0,90000 | 0,9000000000 | 0,3428 | 0,1218 | 0,1736510702 |
| Tsai et al. | 1995 | 36 | 13 | 16 | 15 | 20 | 1,44 | 0,29 | 7,25 | 0,91667 | 0,5625000000 | 0,4533 | 0,0747 | 0,2869181245 |
| James et al. | 1997 | 270 | 116 | 117 | 107 | 153 | 49,87 | 6,76 | 367,95 | 0,99630 | 0,0085470085 | 0,9263 | 0,3817 | 0,0000000000 |
| Westgeest et al. | 1998 | 98 | 10 | 14 | 56 | 84 | 1,25 | 0,36 | 4,34 | 0,95918 | 1,1428571429 | 0,2850 | 0,0355 | 0,2325337341 |
| Kitagawa et al. | 1998 | 131 | 64 | 65 | 52 | 66 | 17,23 | 2,19 | 135,40 | 0,99237 | 0,0153846154 | 0,9013 | 0,3089 | 0,0002635504 |
| Lau et al. | 1998 | 56 | 27 | 34 | 4 | 22 | 17,36 | 4,43 | 68,01 | 0,87500 | 1,4411764706 | 0,2299 | 0,6015 | 0,0000070593 |
| Strata et al. | 1999 | 115 | 55 | 60 | 33 | 55 | 7,33 | 2,53 | 21,22 | 0,95652 | 0,4166666667 | 0,5186 | 0,3732 | 0,0000490555 |
| James et al. | 2001 | 588 | 195 | 196 | 370 | 392 | 11,59 | 1,55 | 86,67 | 0,99830 | 0,0051020408 | 0,9431 | 0,1241 | 0,0008692782 |
| Chen et al. | 2005 | 72 | 31 | 36 | 30 | 36 | 1,24 | 0,34 | 4,50 | 0,93056 | 0,6944444444 | 0,4047 | 0,0386 | 0,2429624922 |
| Parks et al. | 2005 | 506 | 220 | 230 | 256 | 276 | 1,72 | 0,79 | 3,75 | 0,98024 | 0,4347826087 | 0,5097 | 0,0611 | 0,0598564420 |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Berkun et al. | 2009 | 260 | 114 | 120 | 127 | 140 | 1,94 | 0,72 | 5,29 | 0,97692 | 0,3000000000 | 0,5839 | 0,0821 | 0,0816128126 |
| Chen et al. | 2010 | 464 | 81 | 94 | 308 | 370 | 1,25 | 0,66 | 2,39 | 0,97198 | 1,7978723404 | 0,1800 | 0,0320 | 0,1023368848 |
| Draborg et al. | 2012 | 80 | 48 | 60 | 15 | 20 | 1,33 | 0,40 | 4,40 | 0,85000 | 2,4000000000 | 0,1213 | 0,0529 | 0,2137718782 |
| Csuka et al. | 2012 | 646 | 286 | 301 | 310 | 345 | 2,15 | 1,15 | 4,03 | 0,97678 | 0,7475083056 | 0,3873 | 0,0964 | 0,0057414496 |
| Han et al. | 2018 | 192 | 104 | 116 | 68 | 76 | 1,02 | 0,40 | 2,62 | 0,93750 | 1,2413793103 | 0,2652 | 0,0029 | 0,1897224260 |
| Total | | 3599 | 1407 | 1510 | 1768 | 2089 | | | | | | | | |

| | |
|---|---|
| Alpha = | 0,05 |
| Degrees of freedom = | 16 |
| **$X^2$ CRITICAL (k) =** | **26,296** |
| **$X^2$ Calculated (k) =** | **124,72** |

## 2.2. Methods

### 2.2.1. Data analysis

The causal relationship k (I. Barukčić, 2016, 2018c, 2018b, 2019b; K. Barukčić & Barukčić, 2016; K. Barukčić, Barukčić, & Barukčić, 2018) 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 (Pearson, 1900). The *conditio sine qua non* (I. Barukčić, 2016, 2018c, 2018b, 2019b; K. Barukčić & Barukčić, 2016; K. Barukčić et al., 2018) relationship (SINE) was used to proof the hypothesis, *without* EBV *no* SLE. The index of unfairness (I. Barukčić, 2019a) 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.

**Example.**

Gaseous oxygen (A) is vital for human life (C). Under completely gaseous oxygen free conditions, no human being can survive for a longer time. How long can an average human being live without oxygen depends upon circumstances. However, without gaseous oxygen, no human life on our planet. Gaseous oxygen is a necessary condition of human life. In point of fact, without appropriate water (B) no human life (C) too, we can't survive without water (B). Thus far, even if gaseous oxygen is present, if there is no water, we will not survive. Human life can exist only in the presence of appropriate conditions. A risk factor A (i.e. gaseous oxygen), which is necessary condition of an outcome C needs not to be the only necessary condition of an outcome C. Another risk factor B (i. e. water) can be a necessary condition too. How many necessary conditions may determine the outcome C, without one single necessary condition no outcome C.

## 3. Results

### THEOREM 1. WITHOUT EBV VCA IGG ANTIBODY POSITIVITY NO SLE

CLAIM.

Null-Hypothesis: EBV VCA IgG Antibody positivity is a necessary condition of SLE.

Alternative Hypothesis: EBV VCA IgG Antibody positivity is not a necessary condition of SLE.

PROOF.

Many times, it is difficult to test a hypothesis in all people of a population. Due to many reasons, there is a need to draw inferences about phenomena in the population from events observed in a sample. However, no matter how many data a researcher collects, a sample which is inadequate to represent the target population (IOU = +0,274) and an inappropriate sample size may have influence on research outcomes and can compromise the conclusions drawn from the data of a study. Moreover, the widespread belief that large samples are ideal for research is not always true. A large a sample may amplify the detection of differences and emphasizing statistical differences which are not justified. In contrast to a large study, a study with a smaller sample size may not be able to detect an existing difference between study groups. In this context, the central limit theorem is the cornerstone of modern statistics. According to the central limit theorem, if the sample size from the population is sufficiently large (rule of thumb: $n \geq 30$), then the mean of the sample is approximately normally distributed regardless of the population distribution. The publication bias of the studies considered for meta-analysis was more or less acceptable (Average IOU = +0,274). According to the data analyzed (**Table 2**) with a sample size of N=3599 it was not possible (Degrees of freedom =16; $X^2_{Calculated}(SINE)= 12,47$; $X^2_{CRITICAL}(SINE) =26,296$) to reject the null-hypothesis, because $X^2_{Calculated}(SINE) < X^2_{CRITICAL}(SINE)$. We reject the alternative hypothesis and accept the Null-hypothesis: *without* EBV VCA IgG antibody positivity *no* SLE. An EBV infection (detected by EBV VCA IgG) is a necessary condition of SLE.

QUOD ERAT DEMONSTRANDUM.

### THEOREM 2. AN EBV INFECTION IS THE CAUSE OF SLE

CLAIM.

Null-Hypothesis: No causal relationship between EBV and SLE (k = 0).

Alternative Hypothesis: Causal relationship between EBV and SLE ($k \neq 0$).

PROOF.

The studies analyzed (**Table 4**) provided evidence of a significant causal relationship k (n = 3599; degrees of freedom =16; $X^2_{Calculated}$ (k) =124,72; $X^2_{CRITICAL}$ (k) = 26,296). We reject the null-hypothesis and accept the alternative hypothesis because $X^2_{Calculated}$ (k) =124,72 > $X^2_{CRITICAL}$ (k) = 26,296. There is a highly significant causal relationship k between EBV and SLE. The data re-analyzed support the hypothesis too that an EBV infection is a necessary condition (**Table 2**) of SLE. Based on the data analyzed, the conclusion is justified that an *EBV infection is the cause of SLE*.

QUOD ERAT DEMONSTRANDUM.

## 4. Discussion

The etiology of systemic lupus erythematosus is still not well understood. Various risk factors including ultraviolet radiation (Bijl & Kallenberg, 2006; Kirchhof & Dutz, 2014; Kuhn & Beissert, 2005; Kuhn, Wenzel, & Weyd, 2014; Lehmann, Hölzle, Kind, Goerz, & Plewig, 1990; Meller et al., 2005), geographical distribution (Pan et al., 2014; Qian et al., 2014), seasonal distribution (Amit, Molad, Kiss, & Wysenbeek, 1997; Duarte-García, Fang, To, Magder, & Petri, 2012), climate factors (Chiche et al., 2012; Hua-Li, Shi-Chao, De-Shen, Dong, & Hua-Feng, 2011; Léone et al., 1997; Szeto et al., 2008; Yang et al., 2012) such as wind speed, atmospheric pressure, temperature, mean humidity, and precipitation and other (Pan et al., 2019) environmental risk factors (Deapen et al., 1992) are discussed to be involved in the pathogenesis of SLE. However, studies published provided very contradictory results. Various studies provided evidence that especially ultraviolet radiation (UVR) including UVA (wavelength range: 320-400 nm), UVB (wavelength range: 290-320 nm) and UVC (wavelength range: 200-290 nm), is one of the most important environmental risk factors (Bijl & Kallenberg, 2006; Kirchhof & Dutz, 2014; Kuhn & Beissert, 2005; Kuhn et al., 2014; Lehmann et al., 1990; Meller et al., 2005) which is able to induce SLE. In point of fact, studies reported conflicting results on the relationship between UVR and SLE and the role of UVR in the development of SLE remains controversial. First of all, systemic lupus erythematosus is an autoimmune disease with diverse clinical presentation which involves multiple organ systems and not only those parts of human body, which are exposed very often and intensively to UVR (i.e. lupus nephritis). Furthermore, and in contrast to expectation, McGrath et al. (McGrath, Bak, & Michalski, 1987) demonstrated 1987 that low-dose UVR markedly prolonged lupus survival and decreased lupus mortality. Paradoxically, a low-dose, long-term UVA therapy was able to decrease clinical disease activity in SLE significantly (McGrath, 1994, 2005;

McGrath, Martínez-Osuna, & Lee, 1996; Molina & McGrath, 1997, 1997). Thus far, other risk factors then UVR are more likely to provide to the etiology of SLE. Especially EBV has been suspected to be related to SLE. Evans et al. (Evans et al., 1971) were one of the first who were able to report raised antibody titres to EBV in systemic lupus erythematosus patients. Epstein et al. detected (Epstein et al., 1964) the EBV virus in 1964 in cultured Burkitt lymphoma cells. Epstein Barr virus (EBV), is a gamma-herpesvirus which infects at least 90% of the population worldwide (J. I. Cohen, 2000) and is able to cause different clinical syndromes, including mononucleosis (Filatov, 1904; Godt, 2010; Hoagland, 1955; Sprunt & Evans, 1920) or Emil Pfeiffer's (1846–1921) disease (Godt, 2010), multiple sclerosis (I. Barukčić, 2018b; K. Barukčić & Barukčić, 2016), rheumatoid arthritis (K. Barukčić et al., 2018), Hodgkin's disease (I. Barukčić, 2018a) and possibly a number of other malignancies too. Most patients are exposed to EBV by early adulthood. After the primary infection, Epstein-Barr virus establishes latency by persistence for life in long-term memory B cells (Babcock, Decker, Volk, & Thorley-Lawson, 1998) in the peripheral blood of human host. Even if controlled (more or less) by host's immune system, EBV can reactivate later in life to produce different diseases. The severity and presentation of an acute infection with EBV can vary widely ranging from a life-threatening version of mononucleosis (liver damage, splenomegaly) to an asymptomatic infection. In this context, serological markers for EBV infection are often commonly used diagnostic tools for this purpose. However, an Epstein-Barr virus (EBV) infection is accompanied with the fact that IgG-antibodies to Epstein-Barr nuclear antigen 1 (EBNA-1) and IgM- and IgG-antibodies to viral capsid antigen (VCA) can occur simultaneously both during subclinical viral reactivation and in late primary infection (Nystad & Myrmel, 2007) and the interpretation of EBV serologies remains a challenge to some extent. Therefore, under such circumstances, it appears to be a little bit difficult to distinguish a primary EBV infection, a reactivation of latent infection or evidence of a past EBV infection only by means of EBV-specific serology. However, a task which is difficult is therefore not impossible (Linde & Falk, 2007). Klutts et al. (Klutts, Ford, Perez, & Gronowski, 2009) conducted a study with a large population of patients to develop techniques for interpreting multiplexed EBV results. The presence of EBV VCA IgG in the absence of EBV VCA IgM and EBV EBNA- 1 IgG antibodies indicates a past infection with EBNA- 1 IgG loss or non- appearance but equally an acute EBV infection with the early disappearance or delayed onset of EBV VCA IgM (De Paschale et al., 2009). In the present study, EBV VCA IgG positivity was used as an indicator that an individual

investigated is EBV positive. However, EBV VCA IgG is catabolized in patients at a certain rate with half-life of circulating immunoglobulin G (IgG) of roughly 10–21 days (Mankarious et al., 1988) depending on IgG isotype and other factors. Due to this fact, false negative results in this study cannot be excluded.

The validity of any clinical research and thus far of this study too may be affected by chance, generalizability, and bias. There are many hidden biases which can negatively affect the outcome of a study, the sample size is only one of these factors. One should note, however, that the studies included in this meta-analysis have to some extent small sample sizes and laboratory practice is lacking a general standard. Even if EBV is able to generate multiple antibodies in the serum, EBV VCA IgG is generally considered as a sensitive indicator of an exposure to EBV. Since EBV persist for life in memory B cells (Babcock et al., 1998) EBV VCA IgG is used as evidence of EBV positivity. Meanwhile, a number of observations have been made linking EBV to SLE (Chêne et al., 2007; Daibata, Speck, Mulder, & Sairenji, 1994) but it remains uncertain whether there is a causal relationship between the virus and SLE. The reviews on the relationship between EBV and SLE are very rare. In toto, only two studies investigated this relationship. Hanlon et al. (Hanlon et al., 2014) included 25 studies in their meta-analysis of case–control studies while inappropriate studies were not excluded from analysis to a necessary extent. Still, Hanlon et al. (Hanlon et al., 2014) found a significant association between SLE and serological markers of an EBV VCA IgG (OR = 2.08, 95% CI 1.15 to 3.76). Li et al. (Li et al., 2019) meta-analysed 19 studies, including studies with self-contradictory data too, and found only a significant association between EBV sero-positivity and SLE (OR: 3.86, 95% CI 1.52–9.83, p = 0.005) based on VCA antibodies. Both reviews failed to provide evidence of a cause effect relationship between EBV and SLE. In this review, at the end 27 studies with a sample size of n = 5566 were identified for a review. The strengths of this meta-analysis includes the search strategy and the absence of self-contradictory data in the analysis. In toto, 11 studies with a sample size of n = 1967 provided self-contradictory data and were not considered for a meta-analysis even if all of these studies but the study of Vista et al. 2017 (Vista et al., 2017) supported the Null-hypothesis: *without* EBV infection *no* SLE (**Table 2**). However it is remarkable and necessary to make an effort to pay attention to the fact that the studies analyzed failed to provide evidence of a significant conditio per quam relationship between EBV and SLE which is highly logical and additionally supports the findings of this study. In summary, the evidence of the relationship between EBV and SLE is at the end probably stronger then suggested by

the results of this study. The analysis of the causal relationship between EBV and SLE is grounded on 16 studies with a sample size of n = 3599. The data of the studies analyzed support the alternative hypothesis that there is a cause effect relationship between EBV and SLE (**Table 4**). Taken together, since *without* an EBV infection *no* SLE occurs (**Table 2**), the conclusion is justified that EBV is the cause of SLE. This meta-analysis of case–control studies investigating the causal relationship between SLE and EBV VCA IgG as a serological marker of an EBV infection is, to our knowledge, the first study which provides clear significant evidence of a cause effect relationship between EBV and SLE. While this study focused on EBV VCA IgG indicator of an EBV infection, future studies are warranted and should investigate other markers of an EBV positivity to confirm or refute the findings of this study.

## 5. Conclusion

In summary, these findings support the hypothesis that *without* an EBV infection *no* SLE, while there is a significant cause effect relationship between EBV and SLE too. In conclusion, the findings of this review provide clear support for the hypothesis that *EBV is not only a cause but the cause of SLE*.

## Acknowledgements

The open source, independent and non-profit **Zotero Citation Manager** was used to create and manage references and bibliographies.

## References

Amit, M., Molad, Y., Kiss, S., & Wysenbeek, A. J. “Seasonal variations in manifestations and activity of systemic lupus erythematosus.” *British Journal of Rheumatology* 36.4 (1997): 449–452. [PMID: 9159538]

Babcock, G. J., Decker, L. L., Volk, M., & Thorley-Lawson, D. A. “EBV persistence in memory B cells in vivo.” *Immunity* 9.3 (1998): 395–404. [PMID: 9768759]

Barukčić, I. “Epstein Bar Virus—The Cause of Hodgkin’s Lymphoma.” *Journal of Biosciences and Medicines* 06.01 (2018): 75–100. https://doi.org/10.4236/jbm.2018.61008.

Barukčić, I. “Epstein-Barr virus is the cause of multiple sclerosis.” *International Journal of Current Medical and Pharmaceutical Research* 4.9 (A) (2018): 3674–3682. https://doi.org/10.24327/23956429.ijcmpr20180538.

Barukčić, I. “Helicobacter Pylori is the Cause of Gastric Cancer.” *Modern Health Science* 1.1 (2018): 43–50. https://doi.org/10.30560/mhs.v1n1p43.

Barukčić, I. “Index of Unfairness.” *Modern Health Science* 2.1 (2019): p22. https://doi.org/10.30560/mhs.v2n1p22.

Barukčić, I. “Smoking of tobacco is the cause of human lung cancer.” *Journal of Drug Delivery and Therapeutics* 9.1-s (2019): 148–160. https://doi.org/10.22270/jddt.v9i1-s.2273.

Barukčić, I. “The Mathematical Formula of the Causal Relationship k.” *International Journal of Applied Physics and Mathematics* 6.2 (2016): 45–65. https://doi.org/10.17706/ijapm.2016.6.2.45-65.

Barukčić, K., & Barukčić, I. “Epstein Barr Virus—The Cause of Multiple Sclerosis.” *Journal of Applied Mathematics and Physics* 04.06 (2016): 1042–1053. https://doi.org/10.4236/jamp.2016.46109.

Barukčić, K., Barukčić, J. P., & Barukčić, I. “Epstein-Barr virus is the cause of rheumatoid arthritis.” *Romanian journal of rheumatology* 27.4 (2018): 148–163. Retrieved from https://view.publitas.com/amph/rjr_2018_4_art-02/page/1.

Berkun, Y., Zandman-Goddard, G., Barzilai, O., Boaz, M., Sherer, Y., Larida, B., … Shoenfeld, Y. “Infectious antibodies in systemic lupus erythematosus patients.” *Lupus* 18.13 (2009): 1129–1135. https://doi.org/10.1177/0961203309345729. [PMID: 19880558]

Bijl, M., & Kallenberg, C. G. M. “Ultraviolet light and cutaneous lupus.” *Lupus* 15.11 (2006): 724–727. https://doi.org/10.1177/0961203306071705. [PMID: 17153842]

Broccolo, F., Drago, F., Cassina, G., Fava, A., Fusetti, L., Matteoli, B., … Malnati, M. S. “Selective reactivation of human herpesvirus 6 in patients with autoimmune connective tissue diseases: HHV-6 Reactivation in Autoimmune Diseases.” *Journal of Medical Virology* 85.11 (2013): 1925–1934. https://doi.org/10.1002/jmv.23670.

Chen, C.-J., Lin, K.-H., Lin, S.-C., Tsai, W.-C., Yen, J.-H., Chang, S.-J., … Liu, H.-W. “High prevalence of immunoglobulin A antibody against Epstein-Barr virus capsid antigen in adult patients with lupus with disease flare: case control studies.” *The Journal of Rheumatology* 32.1 (2005): 44–47. [PMID: 15630723]

Chen, D.-Y., Chen, Y.-M., Lan, J.-L., Chen, H.-H., Hsieh, C.-W., Wey, S.-J., & Lu, J. J.-Y. “Polymyositis/dermatomyositis and nasopharyngeal carcinoma: the Epstein-Barr virus connection?” *Journal of Clinical Virology: The Official Publication of the Pan American Society for Clinical Virology* 49.4 (2010): 290–295. https://doi.org/10.1016/j.jcv.2010.08.015. [PMID: 20934910]

Chêne, A., Donati, D., Guerreiro-Cacais, A. O., Levitsky, V., Chen, Q., Falk, K. I., … Bejarano, M. T. “A Molecular Link between Malaria and Epstein–Barr Virus Reactivation.” *PLoS Pathogens* 3.6 (2007): e80. https://doi.org/10.1371/journal.ppat.0030080.

Chiche, L., Jourde, N., Ulmann, C., Mancini, J., Darque, A., Bardin, N., … Bornet, C. “Seasonal variations of systemic lupus erythematosus flares in southern France.” *European Journal of Internal Medicine* 23.3 (2012): 250–254. https://doi.org/10.1016/j.ejim.2011.12.006. [PMID: 22385883]

Chougule, D., Nadkar, M., Rajadhyaksha, A., Pandit-Shende, P., Surve, P., Dawkar, N., … Pradhan, V. “Association of clinical and serological parameters of systemic lupus erythematosus patients with Epstein-Barr virus antibody profile.” *Journal of Medical Virology* 90.3 (2018): 559–563. https://doi.org/10.1002/jmv.24904. [PMID: 28734074]

Cohen, A. S., Reynolds, W. E., & Franklin, E. C. “Preliminary criteria for the classification of systemic lupus erythematosus.” *Bull Rheum Dis* 21 (1971): 643–648.

Cohen, J. I. “Epstein-Barr virus infection.” *The New England Journal of Medicine* 343.7 (2000): 481–492. https://doi.org/10.1056/NEJM200008173430707. [PMID: 10944566]

Csuka, D., Simon, D., Hóbor, R., Uray, K., Prohászka, Z., Bánlaki, Z., … Füst, G. “Serum concentration of immunoglobulin G-type antibodies against the whole Epstein-Barr nuclear antigen 1 and its aa35-58 or aa398-404 fragments in the sera of patients with systemic lupus erythematosus and multiple sclerosis.” *Clinical and Experimental Immunology* 171.3 (2013): 255–262. https://doi.org/10.1111/cei.12022. [PMID: 23379431] [PMCID: PMC3569532]

Daibata, M., Speck, S. H., Mulder, C., & Sairenji, T. “Regulation of the BZLF1 Promoter of Epstein-Barr Virus by Second Messengers in Anti-immunoglobulin-Treated B Cells.” *Virology* 198.2 (1994): 446–454. https://doi.org/10.1006/viro.1994.1056.

De Paschale, M., Agrappi, C., Manco, M. T., Mirri, P., Viganò, E. F., & Clerici, P. “Seroepidemiology of EBV and interpretation of the ‘isolated VCA IgG’ pattern.” *Journal of Medical Virology* 81.2 (2009): 325–331. https://doi.org/10.1002/jmv.21373. [PMID: 19107979]

Deapen, D., Escalante, A., Weinrib, L., Horwitz, D., Bachman, B., Roy-Burman, P., … Mack, T. M. “A revised estimate of twin concordance in systemic lupus erythematosus.” *Arthritis and Rheumatism* 35.3 (1992): 311–318. [PMID: 1536669]

Draborg, A. H., Jørgensen, J. M., Müller, H., Nielsen, C. T., Jacobsen, S., Iversen, L. V., … Duus, K. “Epstein-Barr virus early antigen diffuse (EBV-EA/D)-directed immunoglobulin A antibodies in systemic lupus erythematosus patients.” *Scandinavian Journal of Rheumatology* 41.4 (2012): 280–289. https://doi.org/10.3109/03009742.2012.665944. [PMID: 22646970]

Draborg, Anette Holck, Jacobsen, S., Westergaard, M., Mortensen, S., Larsen, J. L., Houen, G., & Duus, K. “Reduced response to Epstein-Barr virus antigens by T-cells in systemic lupus erythematosus patients.” *Lupus Science & Medicine* 1.1 (2014): e000015. https://doi.org/10.1136/lupus-2014-000015. [PMID: 25396062] [PMCID: PMC4225738]

Draborg, Anette Holck, Sandhu, N., Larsen, N., Lisander Larsen, J., Jacobsen, S., & Houen, G. “Impaired Cytokine Responses to Epstein-Barr Virus Antigens in Systemic Lupus Erythematosus Patients.” *Journal of Immunology Research* 2016 (2016): 6473204. https://doi.org/10.1155/2016/6473204. [PMID: 27110576] [PMCID: PMC4826706]

Duarte-García, A., Fang, H., To, C. H., Magder, L. S., & Petri, M. “Seasonal variation in the activity of systemic lupus erythematosus.” *The Journal of Rheumatology* 39.7 (2012): 1392–1398. https://doi.org/10.3899/jrheum.111196. [PMID: 22660806] [PMCID: PMC3597113]

Epstein, M. A., Achong, B. G., & Barr, Y. M. “Virus Particles in Cultured Lymphoblasts from Burkitt’s Lymphoma.” *Lancet* 283.7335 (1964): 702–703. https://doi.org/10.1016/S0140-6736(64)91524-7.

Esen, B. A., Yılmaz, G., Uzun, S., Ozdamar, M., Aksözek, A., Kamalı, S., … Inanç, M. "Serologic response to Epstein-Barr virus antigens in patients with systemic lupus erythematosus: a controlled study." *Rheumatology International* 32.1 (2012): 79–83. https://doi.org/10.1007/s00296-010-1573-4. [PMID: 20661740]

Evans, A. S., Rothfield, N. F., & Niederman, J. C. "Raised antibody titres to E.B. virus in systemic lupus erythematosus." *Lancet (London, England)* 1.7691 (1971): 167–168. [PMID: 4102189]

Filatov, N. F. Semeiology and diagnosis of diseases of children, together with a therapeutic index. Chicago. Retrieved from https://catalog.hathitrust.org/Record/001586896.

Godt, M. Der Wiesbadener Arzt und Entdecker des Drüsenfiebers Dr. Emil Pfeiffer (1846 - 1921): Leben und Werk. Duisburg Köln: WiKu.

Gordon, C., & Isenberg, D. (Eds.). Systemic lupus erythematosus. First edition. Oxford: Oxford University Press.

Han, L., Zhang, Y., Wang, Q., Xin, M., Yang, K., Lei, K., & Sun, M. "Epstein-Barr virus infection and type I interferon signature in patients with systemic lupus erythematosus." *Lupus* (2018): 961203317753069. https://doi.org/10.1177/0961203317753069. [PMID: 29338588]

Hanlon, P., Avenell, A., Aucott, L., & Vickers, M. A. "Systematic review and meta-analysis of the sero-epidemiological association between Epstein-Barr virus and systemic lupus erythematosus." *Arthritis Research & Therapy* 16.1 (2014): R3. https://doi.org/10.1186/ar4429. [PMID: 24387619] [PMCID: PMC3978841]

Hargraves, M. M., Richmond, H., & Morton, R. "Presentation of two bone marrow elements; the tart cell and the L.E. cell." *Proceedings of the Staff Meetings. Mayo Clinic* 23.2 (1948): 25–28. [PMID: 18921142]

Helyer, B. J., & Howie, J. B. "Renal disease associated with positive lupus erythematosus tests in a cross-bred strain of mice." *Nature* 197 (1963): 197. [PMID: 13953664]

Hench, P. S., Kendall, E. C., Slocumb, C. H., & Polley, H. F. "The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone; compound E) and of pituitary adrenocorticotropic hormone on rheumatoid arthritis." *Proceedings of the Staff Meetings. Mayo Clinic* 24.8 (1949): 181–197. [PMID: 18118071]

Hoagland, R. J. "The transmission of infectious mononucleosis." *The American Journal of the Medical Sciences* 229.3 (1955): 262–272. [PMID: 14349955]

Hua-Li, Z., Shi-Chao, X., De-Shen, T., Dong, L., & Hua-Feng, L. "Seasonal distribution of active systemic lupus erythematosus and its correlation with meteorological factors." *Clinics (Sao Paulo, Brazil)* 66.6 (2011): 1009–1013. https://doi.org/10.1590/s1807-59322011000600015. [PMID: 21808867] [PMCID: PMC3129944]

Huggins, M. L., Todd, I., & Powell, R. J. "Reactivation of Epstein-Barr virus in patients with systemic lupus erythematosus." *Rheumatology International* 25.3 (2005): 183–187. https://doi.org/10.1007/s00296-003-0420-2. [PMID: 14666378]

James, J. A., Kaufman, K. M., Farris, A. D., Taylor-Albert, E., Lehman, T. J., & Harley, J. B. “An increased prevalence of Epstein-Barr virus infection in young patients suggests a possible etiology for systemic lupus erythematosus.” *The Journal of Clinical Investigation* 100.12 (1997): 3019–3026. https://doi.org/10.1172/JCI119856. [PMID: 9399948] [PMCID: PMC508514]

James, J. A., Neas, B. R., Moser, K. L., Hall, T., Bruner, G. R., Sestak, A. L., & Harley, J. B. “Systemic lupus erythematosus in adults is associated with previous Epstein-Barr virus exposure.” *Arthritis and Rheumatism* 44.5 (2001): 1122–1126. https://doi.org/10.1002/1529-0131(200105)44:5<1122::AID-ANR193>3.0.CO;2-D. [PMID: 11352244]

Kanegane, H., Wakiguchi, H., Kanegane, C., Kurashige, T., & Tosato, G. “Viral Interleukin- 10 in Chronic Active Epstein- Barr Virus Infection.” *The Journal of Infectious Diseases* 176.1 (1997): 254–257. https://doi.org/10.1086/517260.

Kaposi, M. “Neue Beiträge zurKenntniss des Lupus erythematosus.” *Archiv für Dermatologie und Syphilis* 4.1 (1872): 36–78. https://doi.org/10.1007/BF01921090.

Kirchhof, M. G., & Dutz, J. P. “The immunopathology of cutaneous lupus erythematosus.” *Rheumatic Diseases Clinics of North America* 40.3 (2014): 455–474, viii. https://doi.org/10.1016/j.rdc.2014.04.006. [PMID: 25034156]

Kitagawa, H., Iho, S., Yokochi, T., & Hoshino, T. “Detection of antibodies to the Epstein-Barr virus nuclear antigens in the sera from patients with systemic lupus erythematosus.” *Immunology Letters* 17.3 (1988): 249–252. [PMID: 2836302]

Klutts, J. S., Ford, B. A., Perez, N. R., & Gronowski, A. M. “Evidence-Based Approach for Interpretation of Epstein-Barr Virus Serological Patterns.” *Journal of Clinical Microbiology* 47.10 (2009): 3204–3210. https://doi.org/10.1128/JCM.00164-09.

Kuhn, A., & Beissert, S. “Photosensitivity in lupus erythematosus.” *Autoimmunity* 38.7 (2005): 519–529. https://doi.org/10.1080/08916930500285626. [PMID: 16373257]

Kuhn, A., Wenzel, J., & Weyd, H. “Photosensitivity, apoptosis, and cytokines in the pathogenesis of lupus erythematosus: a critical review.” *Clinical Reviews in Allergy & Immunology* 47.2 (2014): 148–162. https://doi.org/10.1007/s12016-013-8403-x. [PMID: 24420508]

Labonte, A. C., Kegerreis, B., Geraci, N. S., Bachali, P., Madamanchi, S., Robl, R., … Grammer, A. C. “Identification of alterations in macrophage activation associated with disease activity in systemic lupus erythematosus.” *PLOS ONE* 13.12 (2018): e0208132. https://doi.org/10.1371/journal.pone.0208132.

Lau, C. S., Yuen, K. Y., Chan, K. H., & Wong, R. W. “Lack of evidence of active lytic replication of Epstein-Barr and cytomegaloviruses in patients with systemic lupus erythematosus.” *Chinese Medical Journal* 111.7 (1998): 660–665. [PMID: 11245059]

Lehmann, P., Hölzle, E., Kind, P., Goerz, G., & Plewig, G. “Experimental reproduction of skin lesions in lupus erythematosus by UVA and UVB radiation.” *Journal of the American Academy of Dermatology* 22.2 Pt 1 (1990): 181–187. [PMID: 2179293]

Léone, J., Pennaforte, J. L., Delhinger, V., Detour, J., Lefondre, K., Eschard, J. P., & Etienne, J. C. “[Influence of seasons on risk of flare-up of systemic lupus: retrospective

study of 66 patients].” *La Revue De Medecine Interne* 18.4 (1997): 286–291. [PMID: 9161555]

Leonhardt, T. “FAMILY STUDIES IN SYSTEMIC LUPUS ERYTHEMATOSUS.” *Acta Medica Scandinavica* 176 (1964): SUPPL 416:1+. [PMID: 14164860]

Li, Z.-X., Zeng, S., Wu, H.-X., & Zhou, Y. “The risk of systemic lupus erythematosus associated with Epstein-Barr virus infection: a systematic review and meta-analysis.” *Clinical and Experimental Medicine* 19.1 (2019): 23–36. https://doi.org/10.1007/s10238-018-0535-0. [PMID: 30361847] [PMCID: PMC6394567]

Linde, A., & Falk, K. I. Chapter 103 Epstein-Barr Virus, pp. 1564–1573. Manual of clinical microbiology. 9th ed. Washington, D.C: ASM Press.

Mankarious, S., Lee, M., Fischer, S., Pyun, K. H., Ochs, H. D., Oxelius, V. A., & Wedgwood, R. J. “The half-lives of IgG subclasses and specific antibodies in patients with primary immunodeficiency who are receiving intravenously administered immunoglobulin.” *The Journal of Laboratory and Clinical Medicine* 112.5 (1988): 634–640. [PMID: 3183495]

Marchini, B., Dolcher, M. P., Sabbatini, A., Klein, G., & Migliorini, P. “Immune response to different sequences of the EBNA I molecule in Epstein-Barr virus-related disorders and in autoimmune diseases.” *Journal of Autoimmunity* 7.2 (1994): 179–191. https://doi.org/10.1006/jaut.1994.1014. [PMID: 7518683]

McGrath, H. “Elimination of anticardiolipin antibodies and cessation of cognitive decline in a UV-A1-irradiated systemic lupus erythematosus patient.” *Lupus* 14.10 (2005): 859–861. https://doi.org/10.1191/0961203305lu2164cr. [PMID: 16304728]

McGrath, H. “Ultraviolet-A1 irradiation decreases clinical disease activity and autoantibodies in patients with systemic lupus erythematosus.” *Clinical and Experimental Rheumatology* 12.2 (1994): 129–135. [PMID: 8039279]

McGrath, H., Bak, E., & Michalski, J. P. “Ultraviolet-A light prolongs survival and improves immune function in (New Zealand black x New Zealand white)F1 hybrid mice.” *Arthritis and Rheumatism* 30.5 (1987): 557–561. [PMID: 3593437]

McGrath, H., Martínez-Osuna, P., & Lee, F. A. “Ultraviolet-A1 (340-400 nm) irradiation therapy in systemic lupus erythematosus.” *Lupus* 5.4 (1996): 269–274. https://doi.org/10.1177/096120339600500405. [PMID: 8869897]

Meller, S., Winterberg, F., Gilliet, M., Müller, A., Lauceviciute, I., Rieker, J., … Homey, B. “Ultraviolet radiation-induced injury, chemokines, and leukocyte recruitment: An amplification cycle triggering cutaneous lupus erythematosus.” *Arthritis and Rheumatism* 52.5 (2005): 1504–1516. https://doi.org/10.1002/art.21034. [PMID: 15880822]

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. “Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.” *Annals of internal medicine* 151.4 (2009): 264–964. [PMID: 19622511]

Molina, J. F., & McGrath, H. “Longterm ultraviolet-A1 irradiation therapy in systemic lupus erythematosus.” *The Journal of Rheumatology* 24.6 (1997): 1072–1074. [PMID: 9195511]

Morteo, O. G., Franklin, E. C., Mcewen, C., Phythyon, J., & Tanner, M. “Studies of relatives of patients with systemic lupus erythematosus.” *Arthritis and Rheumatism* 4 (1961): 356–363. [PMID: 13772948]

Ngou, J., & Segondy, M. “Immunoblotting reactivity of sera from patients with autoimmune connective tissue diseases against Epstein-Barr nuclear antigen (EBNA) polypeptides.” *Serodiagnosis and Immunotherapy in Infectious Disease* 8.2 (1996): 105–108. https://doi.org/10.1016/S0888-0786(96)80008-4.

Niller, H. H., Wolf, H., & Minarovits, J. “Regulation and dysregulation of Epstein–Barr virus latency: Implications for the development of autoimmune diseases.” *Autoimmunity* 41.4 (2008): 298–328. https://doi.org/10.1080/08916930802024772.

Nystad, T. W., & Myrmel, H. “Prevalence of primary versus reactivated Epstein-Barr virus infection in patients with VCA IgG-, VCA IgM- and EBNA-1-antibodies and suspected infectious mononucleosis.” *Journal of Clinical Virology: The Official Publication of the Pan American Society for Clinical Virology* 38.4 (2007): 292–297. https://doi.org/10.1016/j.jcv.2007.01.006. [PMID: 17336144]

Olsen, N. J., & Karp, D. R. “Autoantibodies and SLE—the threshold for disease.” *Nature Reviews Rheumatology* 10.3 (2014): 181–186. https://doi.org/10.1038/nrrheum.2013.184.

Pan, Q., Chen, J., Guo, L., Lu, X., Liao, S., Zhao, C., … Liu, H. “Mechanistic insights into environmental and genetic risk factors for systemic lupus erythematosus.” *American Journal of Translational Research* 11.3 (2019): 1241–1254. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6456562/. [PMID: 30972159] [PMCID: PMC6456562]

Pan, Q., Li, Y., Ye, L., Deng, Z., Li, L., Feng, Y., … Liu, H. “Geographical distribution, a risk factor for the incidence of lupus nephritis in China.” *BMC nephrology* 15 (2014): 67. https://doi.org/10.1186/1471-2369-15-67. [PMID: 24885458] [PMCID: PMC4013059]

Parks, C. G., Cooper, G. S., Hudson, L. L., Dooley, M. A., Treadwell, E. L., St Clair, E. W., … Pandey, J. P. “Association of Epstein-Barr virus with systemic lupus erythematosus: effect modification by race, age, and cytotoxic T lymphocyte-associated antigen 4 genotype.” *Arthritis and Rheumatism* 52.4 (2005): 1148–1159. https://doi.org/10.1002/art.20997. [PMID: 15818712]

Pearson, K. “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 (1900): 157–175.

Qian, G., Ran, X., Zhou, C. X., Deng, D. Q., Zhang, P. L., Guo, Y., … Cai, M. “Systemic lupus erythematosus patients in the low-latitude plateau of China: altitudinal influences.” *Lupus* 23.14 (2014): 1537–1545. https://doi.org/10.1177/0961203314544186. [PMID: 25059490]

Rees, F., Doherty, M., Grainge, M. J., Lanyon, P., & Zhang, W. “The worldwide incidence and prevalence of systemic lupus erythematosus: a systematic review of epidemiological studies.” *Rheumatology (Oxford, England)* 56.11 (2017): 1945–1961. https://doi.org/10.1093/rheumatology/kex260. [PMID: 28968809]

Sprunt, T. P., & Evans, F. A. “Mononuclear leucocytosis in reaction to acute infections (‘infectious mononucleosis’).” *Bulletin of the Johns Hopkins Hospital* 31 (1920): 410–417.

Steinberg, A. D., Kaltreider, H. B., Staples, P. J., Goetzl, E. J., Talal, N., & Decker, J. L. “Cyclophosphamide in lupus nephritis: a controlled trial.” *Annals of Internal Medicine* 75.2 (1971): 165–171. [PMID: 4104337]

Stratta, P., Canavese, C., Ciccone, G., Santi, S., Quaglia, M., Ghisetti, V., … Piccoli, G. “Correlation between cytomegalovirus infection and Raynaud’s phenomenon in lupus nephritis.” *Nephron* 82.2 (1999): 145–154. https://doi.org/10.1159/000045391. [PMID: 10364707]

Szeto, C.-C., Mok, H.-Y., Chow, K.-M., Lee, T.-C., Leung, J. Y.-K., Li, E. K.-M., … Tam, L.-S. “Climatic influence on the prevalence of noncutaneous disease flare in systemic lupus erythematosus in Hong Kong.” *The Journal of Rheumatology* 35.6 (2008): 1031–1037. [PMID: 18398942]

Tazi, I., Fehri, S., Elghrari, K., Ouazzani, T., & Benchemsi, N. “Systemic lupus erythematosus and Epstein-Barr virus. (Article in French).” *Eastern Mediterranean Health Journal = La Revue De Sante De La Mediterranee Orientale = Al-Majallah Al-Sihhiyah Li-Sharq Al-Mutawassit* 15.3 (2009): 701–708. [PMID: 19731786]

Toussirot, E., & Roudier, J. “Pathophysiological links between rheumatoid arthritis and the Epstein–Barr virus: An update.” *Joint Bone Spine* 74.5 (2007): 418–426. https://doi.org/10.1016/j.jbspin.2007.05.001.

Tsai, Y. T., Chiang, B. L., Kao, Y. F., & Hsieh, K. H. “Detection of Epstein-Barr virus and cytomegalovirus genome in white blood cells from patients with juvenile rheumatoid arthritis and childhood systemic lupus erythematosus.” *International Archives of Allergy and Immunology* 106.3 (1995): 235–240. https://doi.org/10.1159/000236848. [PMID: 7888786]

Us, T., Cetin, E., Kaşifoğlu, N., Kaşifoğlu, T., & Akgün, Y. “Investigation of Epstein-Barr virus and herpes simplex virus markers by serological and molecular methods in patients with rheumatoid arthritis and systemic lupus erythematosus (Article in Turkish).” *Mikrobiyoloji Bulteni* 45.4 (2011): 677–683. [PMID: 22090298]

Vista, E. S., Weisman, M. H., Ishimori, M. L., Chen, H., Bourn, R. L., Bruner, B. F., … James, J. A. “Strong viral associations with SLE among Filipinos.” *Lupus Science & Medicine* 4.1 (2017): e000214. https://doi.org/10.1136/lupus-2017-000214.

Westgeest, A. A., van Loon, A. M., van der Logt, J. T., van de Putte, L. B., & Boerbooms, A. M. “Antiperinuclear factor, a rheumatoid arthritis specific autoantibody: its relation to Epstein-Barr virus.” *The Journal of Rheumatology* 16.5 (1989): 626–630. [PMID: 2547060]

Yang, J., Lu, Y.-W., Pan, H.-F., Tao, J.-H., Zou, Y.-F., Bao, W., & Ye, D.-Q. “Seasonal distribution of systemic lupus erythematosus activity and its correlation with climate

factors." *Rheumatology International* 32.8 (2012): 2393–2399. https://doi.org/10.1007/s00296-011-1971-2. [PMID: 21667078]

Yokochi, T., Yanagawa, A., Kimura, Y., & Mizushima, Y. "High titer of antibody to the Epstein-Barr virus membrane antigen in sera from patients with rheumatoid arthritis and systemic lupus erythematosus." *The Journal of Rheumatology* 16.8 (1989): 1029–1032. [PMID: 2555505]

Zhang, X., Li, B., Liu, Y., & Jiang, M. "Clinical study on antibodies against EBV in sera of patients with rheumatoid arthritis (Article in Chinese)." *Zhongguo Yi Xue Ke Xue Yuan Xue Bao. Acta Academiae Medicinae Sinicae* 21.1 (1999): 8–12. [PMID: 12569633]