Title: Shame, Name, Give Up the Game? Three Approaches to Uncertainty

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Abstract: There are three approaches to uncertainty in autoimmune diseases: deny, solve, and accept. Denial hurts patients, physicians, and society, but is probably common due to its short-term time efficiency for physicians and minimisation of cognitive dissonance when belief (“doctors help people”) conflicts with behavior (“I don’t help this person”). Solving helps patients who are correctly classified, but approaching uncertainty primarily as a classification problem creates “winners” (patients who are so helped) and “losers” (patients with still-uncertain diseases). Excluding patients with uncertain diseases from study perpetuates their invisibility. But accepting uncertainty as part of the process in this realm is compatible with improving diagnosis (solving). Combining these latter two approaches in a new, more inclusive way of thinking about autoimmunity suggests a broad, preventive care-focused research agenda.

Keywords: Uncertainty; systemic lupus erythematosus (SLE); undifferentiated connective tissue disorder (UCTD); difficult diagnosis; prevention.

What is going on “when the disease has no name”? As a family member and patient, I have observed three main cognitive strategies physicians use to grapple with uncertainty. Some approach it primarily (1) as a threat, others (2) as a classification problem, and others (3) as an ongoing part of health and disease processes. Applying cognitive science insights into why and how uncertainty sometimes threatens physicians underscores the importance of the current movement in rheumatology toward the latter two modes of grappling with it. Both are necessary, because approaching uncertainty as a classification problem has pros and cons.

On one hand, improving classification of cases that are uncertain because they are anomalous, early, and/or mild presentations — as in undifferentiated connective tissue disorder (UCTD) or incomplete, latent, preclinical, or prodromal lupus — or simply because they are classically difficult diagnoses like systemic lupus erythematosus (SLE) — has the potential to help more patients access needed care sooner, elevating quality of life and functioning, and preventing potentially irreversible damage. On the other hand, approaching the problem of uncertainty primarily as a classification problem risks simply shifting the threshold of where patients begin being “in” — recognised as ill and deserving of help — versus “out.” The evidence on uncertain cases is insufficient to specify this threshold. Thus, physicians also need to be able to approach uncertainty primarily as part of reality to be accepted rather than (only) a problem to be solved when possible through better classification. This need does not diminish the importance of classification improvements, but rather represents a concurrent shift away from approaching uncertainty as a threat.

The most common treatments for UCTD and SLE, low-dose hydroxychloroquine and prednisone, may dampen disease development, as may lifestyle changes such as avoidance of UV exposure and heat. Low-dose hydroxychloroquine in particular carries very low iatrogenic harm risks, and low-dose prednisone carries relatively low risks while treating most symptomatic autoimmune phenomena. This suggests grappling with uncertainty “when the disease has no name” should include discussion about the possible risks and benefits of these treatment options. In this context, patients should not suffer for years with symptomatic autoimmunity and no appropriate specialised medical treatment offered for it.

But the current focus on diagnostic criteria means precisely that “Organ damage might accrue in a prodromal period prior to a formal diagnosis of SLE being made,”[[1]](#footnote-1) although these treatments can help prevent that damage. At the same time, an online survey of 3,022 self-reported lupus patients found that most (54.1%) reported having been told there was nothing wrong with them or that their symptoms were psychological.”[[2]](#footnote-2) These disconnects seem in part to be products of physicians sometimes approaching uncertainty as threat.

**Uncertainty As Threat**

“Absence of evidence is not evidence of absence,”[[3]](#footnote-3) and uncertainty in diagnosis is not evidence that a patient presenting with symptoms of unknown etiology is actually well or merely psychologically troubled. Why then would physicians frequently dismiss undiagnosed autoimmune disease sufferers as such?

An empirical answer seems at first to make sense. Depression and anxiety often track with rheumatological diseases including SLE[[4]](#footnote-4), but are also substantially more common than them. Self-reported pain and fatigue as well as frequent infections and other such typical complaints can be associated with mental health as well as rheumatological problems. In light of base rates, Occam’s Razor would seem to favor the former explanation.

But this reflects a logical fallacy, because mental health and rheumatological problems are not mutually exclusive. To the contrary, the rate of mental health problems in SLE patients is sufficiently high, and mechanisms (such as inflammation) associated with rheumatological and mental health problems sufficiently overlap, such that the base rate of rheumatological disease in depressed and anxious subpopulations is likely to be higher than in general populations. So what some physicians use as a dismissal may well be a clue.

Here is where cognitive bias may come in: Physicians face time pressures that constrain their abilities to be and remain knowledgeable about everything they are supposed to know (information overload), and patients with complex, gradually developing, heterogeneous conditions such as UCTD and SLE present particularly time-intensive diagnostic puzzles. What is a physician seeing many patients a day along with other responsibilities to do?

Perhaps, faced with these pressures, many physicians experience diagnostic uncertainty as the threat of cognitive dissonance. Ironically, desire to help people and see oneself as helping people as a doctor can underpin this mode as belief (“doctors help people”) conflicts with behavior (“I don’t help this person”). This conflict can be lessened by rejecting the uncertainty itself (“this patient is [definitely] well or crazy”). This cognitive strategy is time-efficient for the individual physician, and protects his or her ego as an expert whose social and legal power comes from knowing about health and disease, insofar as expertise often blurs with certainty.

But it is inefficient (not to mention unpleasant) for the patient, who continues to suffer without appropriate medical help, and society, as patients with unmanaged autoimmunity tend to fare worse than their treated counterparts, with preventable damage causing harm to their families and communities, as well as costing more in healthcare and disability. It is also inefficient for colleagues, who have to deal with the dismissed patients in future interactions. In this way, the cognitive strategy of threat in dealing with diagnostic uncertainty arguably drives physician defection in a collective action problem[[5]](#footnote-5) — a situation in which everyone would be better off cooperating, but enough people choose instead to pursue their immediate self-interest that the behavioral norm undercuts the group’s long-term interests. So it benefits everyone — physicians, patients, and society — when physicians are better able to shift cognitive strategies in dealing with diagnostic uncertainty, away from threat and toward classification and process modes.

Taking patients at their word underpins this shift. Questioning patient credibility of self-reported symptoms undermines the possibility of a therapeutic relationship, increasing the likelihood that both doctor and patient will experience an interaction as threatening. This might contribute to a mistrust spiral in which patients trust medicine and science less. The social implications of such spirals can be weighty: Mistrust of the medical profession predicts parental vaccine hesitancy.[[6]](#footnote-6) In this context, changing the way physicians treat patients “when the disease has no name” has the potential to affect public health.

A new set of consensus guidelines setting out clear management options for uncertain diagnoses might help physicians make this shift. The temptation in devising such guidelines, however, is to again deny the central problem of uncertainty — this time by moving the diagnostic threshold. This has the potential to help many people access needed care sooner, preventing harm. But as a cognitive mode for dealing with uncertainty, it also has the potential to perpetuate the patterns of the threat mode by attempting to solve instead of accepting uncertainty. Uncertain disease is likely an unsolvable problem in rheumatology, given the unpredictable and gradual development of heterogeneous immune dysfunctions and other manifestations, the difficult-to-measure nature of typical complaints such as pain and fatigue, and widely reported difficulties in accessing appropriate specialist care early in disease process.

**Uncertainty As Classification Problem**

Changing the parameters of diagnosable autoimmune disease follows the best available evidence to prevent harm, and is thus well worth doing. For example, prodromal lupus patients treated with hydroxychloroquine or prednisone had delayed classifiable SLE onset, and hydroxychloroquine was also associated with fewer later autoantibody specificities, according to a retrospective study of 130 military personnel.[[7]](#footnote-7) Indeed, this already appears to be standard practice in some places, with the majority of incomplete or potential lupus patients at Brigham and Women’s Hospital (66% of 161 patients)[[8]](#footnote-8) and in the Spanish Rheumatology Society Lupus Registry (around 69% of 345 patients)[[9]](#footnote-9) treated with antimalarial medication. These observations still suggest a substantial minority of affected patients (within the universe of identified patients) miss out on effective preventive treatment for unspecified reasons, suggesting room for improvement through updated consensus guidelines.

Relevant literature tends to emphasise these interventions as lupus interventions[[10]](#footnote-10), focusing on the subset of patients with undifferentiated, early, mild, or prodromal disease who go on to develop diagnosable, differentiated diseases including SLE. This suggests researchers may be placing less value on possible quality of life and functioning improvements for the whole class of symptomatic patients than on preventing disease progression in a more severe subset. But given that undifferentiated disease, too, can disable patients with pain, fatigue, and many of the other same manifestations as diagnosable SLE, this focus might be misplaced from a patient perspective. Given that the difference between undifferentiated and differentiated disease diagnosis can depend entirely on whether patients access the right care at the right time — while disabled, and often after having experienced physician dismissal of their complaints — this focus might also be misplaced in a substantial subset of cases that are missed diagnoses (and misdiagnoses). Given that ambiguity, this focus might also hinder research on autoimmunity by assuming distinctions between patient groups that result in part from differences in the timing and quality of physician-patient interactions, and not from differences in the underlying disease.

In that context, approaching uncertainty as a classification problem will tend to create winners and losers among affected patients. An example illustrates this problem: In a recent article in a top subfield journal, Adamichou et al[[11]](#footnote-11) report testing a machine learning-based model on a sample of patient data from hospital rheumatology clinics. The premise of the tool is that it can assist lupus diagnosis. But by baking in the cognitive distortion of the primacy of the categories of certain lupus and non-lupus patients, its use might keep physicians from learning more about non-lupus, including those for whom diagnosis is uncertain — and keep many of those patients ill and seeking help unsuccessfully. In other words, it seems to assume that diagnostic accuracy is only about quantifiable sensitivity and specificity for a single, binary diagnostic category. Patients with uncertain diagnoses are excluded from the sample, study design, and thinking about the effects of the use of this kind of tool. In this respect, approaching uncertainty as a classification problem is circular: Uncertainty is no longer a problem if all the cases in a given universe are diagnosed.

This kind of research, again, has merit. Improving SLE diagnostic accuracy is important. I used a tool like this one (Stephen Borowitz's Isabel) many years ago in the medical school library to help generate a differential diagnosis that favored SLE when my mom was disabled with a disease without a name. Using that differential to learn more from books, patient support groups, and appropriate specialists, I eventually presented her case synopsis to a rheumatologist who diagnosed and treated her. Hers was not a corner case. But what about such cases?

Batu et al[[12]](#footnote-12) report results from a pediatric cohort study on Adamichou et al’s tool (SLE Risk Probability Index, SLERPI). They find raising the diagnostic threshold in that population decreases sensitivity by around 2% while increasing specificity by around 8%. It is unclear that decreasing sensitivity by a single-digit percentage in order to increase specificity by another single-digit percentage benefits these patients. If clinicians should treat children who score a 7 using this tool the same as they should treat children scoring an 8, raising the threshold to reduce its type II errors while increasing its type I errors would appear to have little practical merit.

In a typical cohort set-up, both Adamichou et al and Bantu et al use patient data from two groups: Those diagnosed with lupus, and those diagnosed with other rheumatologic diseases. Maybe 100% diagnosis rates are the norm in the rheumatology departments of the university hospital clinic samples from which these cohorts were drawn. But I have been to many specialists with my mom, and been to a fair number myself as a patient over the years. Before her SLE and my UCTD diagnoses, physicians usually dismissed us without diagnosis or treatment. Having headed up a lupus patient support group chapter and also heard similar stories from many female friends with other chronic health problems, I believe these sorts of experiences are common. This suggests that perhaps it is a currently accepted research norm to exclude cases without rheumatologic diagnoses from studies like these. That would make uncertain cases invisible to researchers and physicians reading their work. This reflects one danger of approaching uncertainty as a classification problem: It appears to erase it, but in so doing, it may normalise the dismissal of uncertain cases, promoting the threat approach to dealing with uncertainty when some patients inevitably still fall outside the diagnostic bounds. After all, those patients do not appear to exist in the relevant medical literature.

**Uncertainty As Part of Process**

Discussions of the problem of uncertain diagnosis in rheumatology often involve the distinction between classification criteria, used to qualify patients for clinical trials, and diagnostic criteria, used to qualify patients for clinical diagnosis and treatment. This distinction assumes an unproven trade-off between privileging internal validity to treat the most severely affected (e.g., SLE patients with lupus nephritis) over external validity to help the most patients (e.g., SLE patients including those misdiagnosed with UCTD) in a notoriously heterogeneous disease group. It thus exemplifies Alvin Feinstein’s concern that his evidence-based medicine revolution was hijacked by the “distraction” of quantitative models.[[13]](#footnote-13)

Feinstein suggested differentiating between the special collection of data regarded as suitable evidence, and practicing evidence-based medicine.[[14]](#footnote-14) Such data, he noted, derive “almost exclusively from randomised trials and meta-analyses,” and “do not include many types of treatments or patients seen in clinical practice.” Feinstein warned that by calling on doctors to make clinical decisions based on a highly restricted quality and scope of evidence, such work had an “authoritative aura” which “may lead to major abuses that produce inappropriate guidelines or doctrinaire dogmas for clinical practice.” Focus on the boundaries of defined autoimmune diseases using such data leads to precisely such an abuse: Failure to name and treat uncertain cases where such treatment may prevent harm and improve quality of life while posing minimal iatrogenesis risks.

Practicing evidence-based medicine, Feinstein went on, means attending to “such cogent clinical features as severity of symptoms, illness, co-morbidity, and other clinical nuances.” Filling his prescription means recognising that applying somewhat exegetical diagnostic criteria with debatable thresholds causes some patients to suffer without medical help, risking irreversible damage from untreated disease progression in addition to living lives curtailed by common problems such as recurrent infections, intermittently disabling pain and fatigue, and the profound isolation of being unable to say what is wrong. Devising a new, more inclusive way of measuring autoimmunity including uncertain cases suggests a new research agenda that could lead to advances in care, quality of life, and communication for many.

***Research Agenda***

Serum autoimmunity appears to be rising for unknown reasons.[[15]](#footnote-15) This suggests the population of uncertain disease patients may be growing. General population research might include lifestyle and rheumatology questionnaires in an attempt to identify factors that might predispose people to develop practically meaningful symptoms, before clinicians identify disease. This might generate useful insights for diagnosis as well as prevention.

Recent research from the emerging field of nutritional psychiatry establishes that interventions centered on cost-effective nutritional education can lower inflammation and depressive symptoms.[[16]](#footnote-16) The relatively low-risk nature of such interventions make them especially appropriate for studies including patients with uncertain, undifferentiated, and differentiated autoimmune diseases which tend to be characterised by inflammatory processes and are often comorbid with depression and/or anxiety. The importance of diet in lupus has been widely discussed[[17]](#footnote-17), particularly with respect to including “healthy” types of dietary fats[[18]](#footnote-18), probiotics[[19]](#footnote-19), and fresh whole foods (especially fruits and vegetables)[[20]](#footnote-20), caloric restriction or fasting[[21]](#footnote-21), and minimising ultra-processed foods, particularly free sugars[[22]](#footnote-22). But to date, no relevant large-scale randomised trials have been conducted. By blocking on patients’ different disease states and treatments along with demographics like gender within an approximate equalisation rather than true randomisation procedure, researchers could account for the increased within-group heterogeneity resulting from including a wider range of potential autoimmune disease sufferers, while also assessing the extent to which these findings generalise to traditionally-defined rheumatology patients.

Prevention-oriented research including uncertain and undifferentiated cases should also grapple with possible intergenerational effects of autoimmunity, working to identify conditions that may exacerbate or ameliorate them. It appears that in-utero exposures to adverse conditions such as maternal infection and malnutrition can adversely affect offspring, particularly in terms of neurodevelopmental outcomes.[[23]](#footnote-23) Some of the same offspring neurodevelopmental risks (e.g., autism) are associated with maternal autoimmunity.[[24]](#footnote-24) Thus it seems plausible that offering safe, symptomatic treatment for autoimmunity before and during pregnancy might improve offspring outcomes. In the realm of uncertain disease, at what point does the possible cost of iatrogenic harm outweigh the possible benefit of down-regulating maternal autoimmunity during crucial developmental windows? Should pregnant women be screened for autoimmunity, just as they are screened for other conditions that might adversely affect fetal development?

And what about the mistrust created or exacerbated by common patient experiences of going years without needed medical help in spite of asking for it? Might accepting uncertainty as part of the process present its own set of challenges in terms of physician credibility to these and other patients? Or can emphasis on upholding the Hippocratic oath to do no harm trump emphasis on diagnostic accuracy?

As a family member and patient, I think starting from an assumption of patient credibility and accepting uncertainty as part of the process has the potential to enrich therapeutic relationships by reorienting clinical interactions as dialogues in the context of ongoing experiments. But as a scientist, I also understand skepticism toward self-reports, particularly retrospective ones. Maybe there could be more middle ground in practice here, where patients who feel they were not heard or seen in the past have a chance to produce evidence of symptoms that might have occurred in the past. Maybe there should be a different category along the autoimmunity continuum identifying patients who report having met diagnostic criteria unobserved.

By using the scientific method to study the broader universe of cases, this research agenda could help normalise accepting uncertainty as part of the process of diagnosing and treating autoimmune disorders. Just as society has shaped science by demanding certainty, so too can science shape society by accepting uncertainty. The institutional incentive structures of normal medical science, such as grant applications, conference proposals, and academic publication, tend to privilege specificity and staying within narrow parameters that conform to what other people think and are doing.[[25]](#footnote-25) Thus researchers studying diseases like SLE, which often involve long histories of inadequate treatment, underdiagnosis, and eventual progression to more irreversible damage — never seem to meet clinicians who see patients in the process of developing these diseases, before as much recognisable damage is done. Prioritizing mitigating the risks of preventable harm to patients presenting with uncertain autoimmunity might help these experts meet.

**Conclusion**

There is no perfect diagnostic universe. Maximizing one form of accuracy (sensitivity) usually compromises another (specificity). Similarly, there is no risk-free treatment universe. Maximizing prevention usually risks iatrogenic harm when the treatment involves a traditional medical intervention like a pharmaceutical or surgery.

This implies that diseases that have no names will always be with us. There is no diagnostic approach that banishes them, although there is one that makes them someone else’s problem. There is no possible perfect set of guidelines that will prescribe the single best clinical management approach for them, although there are some low-risk treatments for uncertain, mild, or undifferentiated autoimmunity that might be much more broadly appropriate than they are currently applied. Maybe upholding the Hippocratic oath to do no harm in this context means erring more on the side of believing patients and less on prioritising diagnostic accuracy in terms of certainty, no matter the cost.

References

Adamichou C, *et al*. *Ann Rheum Dis* 2021;80:758–766. doi:10.1136/annrheumdis-2020-219069

Al Daabil M, Massarotti EM, Fine A, Tsao H, Ho P, Schur PH, Bermas BL, Costenbader KH. Development of SLE among "potential SLE" patients seen in consultation: long-term follow-up. Int J Clin Pract. 2014 Dec;68(12):1508-13.

Altman, D.G. “Statistics notes: Absence of evidence is not evidence of absence,” *BMJ* 1995;311:485.

Barber, M.R.W., Johnson, S.R., Gladman, D.D. *et al.* Evolving concepts in systemic lupus erythematosus damage assessment. *Nat Rev Rheumatol* (2021).

Batu ED, Kaya Akca U, Basaran O, *et al*. Correspondence on ‘Lupus or not? SLE Risk Probability Index (SLERPI): a simple, clinician-friendly machine-learning-based model to assist the diagnosis of systemic lupus erythematosus.’ *Ann Rheum Dis* (2021).

Berk, M., Williams, L.J., Jacka, F.N. *et al.* So depression is an inflammatory disease, but where does the inflammation come from?. *BMC Med* 11, 200 (2013).

Bourn, R., & James, J. A. (2015). Pre-clinical lupus. *Current opinion in rheumatology*, *27*(5), 433.

Constantin, M., Nita, I. E., Olteanu, R., Constantin, T., Bucur, S., Matei, C., Raducan, A."Significance and impact of dietary factors on systemic lupus erythematosus pathogenesis (Review)". Experimental and Therapeutic Medicine 17.2 (2019): 1085-1090.

Correa-Rodríguez M, Pocovi-Gerardino G, Callejas-Rubio JL, Ríos Fernández R, Martín-Amada M, Cruz-Caparros MG, Medina-Martínez I, Ortego-Centeno N, Rueda-Medina B. Dietary Intake of Free Sugars is Associated with Disease Activity and Dyslipidemia in Systemic Lupus Erythematosus Patients. Nutrients. 2020 Apr 15;12(4):1094. doi: 10.3390/nu12041094. PMID: 32326626; PMCID: PMC7231002.

Daly R, Partovi R, Davidson P. Lupus Diagnosis: Process and Patient Experience [abstract]. *Arthritis Rheumatol.* 2017; 69 (suppl 10). https://acrabstracts.org/abstract/lupus-diagnosis-process-and-patient-experience/. Accessed May 22, 2021.

Dinse GE, Parks CG, Weinberg CR, Co CA, Wilkerson J, Zeldin DC, Chan EKL, Miller FW. 2020. Increasing prevalence of antinuclear antibodies in the United States. Arthritis Rheum; doi: 10.1002/art.41214 [Online 8 April 2020].

Feinstein, A.R. “Clinical Judgment” revisited: the distraction of quantitative models. *Ann. Intern. Med.,* 120, 799-805 (1994).

Feinstein, A.R., & Horwitz, R.I. Problems in the “Evidence” of “Evidence-Based Medicine.” *Am. J. Med.* 103, 529-535 (1997)

Figueiredo-Braga, M., et al, “Depression and anxiety in systemic lupus erythematosus,” [Medicine (Baltimore).](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6076116/) 2018 Jul; 97(28): e11376.

Jacka, F.N., O’Neil, A., Opie, R. et al. A randomised controlled trial of dietary improvement for adults with major depression (the ‘SMILES’ trial). BMC Med 15, 23 (2017). <https://doi.org/10.1186/s12916-017-0791-y>

James et al, “Hydroxychloroquine sulfate treatment is associated with later onset of systemic lupus erythematosus,” *Lupus* (2007) 16, 401-409.

Klack K, Bonfa E, Borba Neto EF. Diet and nutritional aspects in systemic lupus erythematosus. Rev Bras Reumatol. 2012 May-Jun;52(3):384-408. English, Portuguese. PMID: 22641593.

Kolata, G. “Grant System Leads Cancer Researchers to Play It Safe,” *New York Times,* June 28, 2009.

Leiba A, Amital H, Gershwin ME, Shoenfeld Y. Diet and lupus. Lupus. 2001;10(3):246-8. doi: 10.1191/096120301674681790. PMID: 11315362.

Liu Y, Yu Y, Matarese G, La Cava A. Fasting-induced hypoleptinemia expands functional regulatory T cells in systemic lupus erythematosus. J Immunol. 2012 Mar 1;188(5):2070-3. doi: 10.4049/jimmunol.1102835. Epub 2012 Jan 30. PMID: 22291185; PMCID: PMC3288569.

Mu, Q., Zhang, H., Liao, X. *et al.* Control of lupus nephritis by changes of gut microbiota. *Microbiome* 5, 73 (2017). https://doi.org/10.1186/s40168-017-0300-8

Olson, Mancur. The Logic of Collective Action: Public Goods and the Theory of Groups, Second Printing with a New Preface and Appendix. United Kingdom, Harvard University Press, 1971.

Parletta, N., Zarnowiecki, D., Cho, J., Wilson, A., Bogomolova, S., Villani, A., ... & O'Dea, A. (2018). A Mediterranean-style dietary intervention supplemented with fish oil improves diet quality and mental health in people with depression: A randomised controlled trial (HELFIMED). Journal of the Australasian College of Nutritional and Environmental Medicine, 37(1), 6-18.

Reuben R, Aitken D, Freedman JL, Einstein G (2020) Mistrust of the medical profession and higher disgust sensitivity predict parental vaccine hesitancy. PLoS ONE 15(9): e0237755. https://doi.org/10.1371/journal.pone.0237755

Rúa-Figueroa Í, Richi P, López-Longo FJ, Galindo M, Calvo-Alén J, Olivé-Marqués A, Loza-Santamaría E, Vicente SP, Erausquin C, Tomero E, Horcada L, Uriarte E, Sánchez-Atrio A, Rosas J, Montilla C, Fernández-Nebro A, Rodríguez-Gómez M, Vela P, Blanco R, Freire M, Silva L, Díez-Álvarez E, Ibáñez-Barceló M, Zea A, Narváez J, Martínez-Taboada V, Marenco JL, de Castro MF, Fernández-Berrizbeitia O, Hernández-Beriain JÁ, Gantes M, Hernández-Cruz B, Pérez-Venegas JJ, Pecondón Á, Marras C, Carreira P, Bonilla G, Torrente V, Castellví I, Alegre J, Moreno M, Raya E, de la Peña PG, Vázquez T, Aguirre Á, Quevedo V, Pego-Reigosa JM; EAS-SER (Systemic Diseases Study Group of the Spanish Society of Rheumatology). Comprehensive description of clinical characteristics of a large systemic lupus erythematosus cohort from the Spanish Rheumatology Society Lupus Registry (RELESSER) with emphasis on complete versus incomplete lupus differences. Medicine (Baltimore). 2015 Jan;94(1):e267.

Zerbo, O., Qian, Y., Yoshida, C. *et al.* Maternal Infection During Pregnancy and Autism Spectrum Disorders. *J Autism Dev Disord* 45, 4015–4025 (2015). <https://doi.org/10.1007/s10803-013-2016-3>

Zhu, Z., Tang, S., Deng, X., & Wang, Y. “Maternal Systemic Lupus Erythematosus, Rheumatoid Arthritis, and Risk for Autism Spectrum Disorders in Offspring: A Meta‑analysis.” *Journal of Autism and Developmental Disorders* (2020) 50:2852–2859 <https://doi.org/10.1007/s10803-020-04400-y>

1. Barber, M.R.W., Johnson, S.R., Gladman, D.D. *et al.* Evolving concepts in systemic lupus erythematosus damage assessment. *Nat Rev Rheumatol* (2021). [↑](#footnote-ref-1)
2. Daly R, Partovi R, Davidson P. Lupus Diagnosis: Process and Patient Experience [abstract]. *Arthritis Rheumatol.* 2017; 69 (suppl 10). https://acrabstracts.org/abstract/lupus-diagnosis-process-and-patient-experience/. Accessed May 22, 2021. [↑](#footnote-ref-2)
3. Altman, D.G. “Statistics notes: Absence of evidence is not evidence of absence,” *BMJ* 1995;311:485. [↑](#footnote-ref-3)
4. Figueiredo-Braga, M., et al, “Depression and anxiety in systemic lupus erythematosus,” [Medicine (Baltimore).](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6076116/) 2018 Jul; 97(28): e11376. [↑](#footnote-ref-4)
5. Olson, Mancur. The Logic of Collective Action: Public Goods and the Theory of Groups, Second Printing with a New Preface and Appendix. United Kingdom, Harvard University Press, 1971. [↑](#footnote-ref-5)
6. Reuben R, Aitken D, Freedman JL, Einstein G (2020) Mistrust of the medical profession and higher disgust sensitivity predict parental vaccine hesitancy. PLoS ONE 15(9): e0237755. https://doi.org/10.1371/journal.pone.0237755 [↑](#footnote-ref-6)
7. James et al, “Hydroxychloroquine sulfate treatment is associated with later onset of systemic lupus erythematosus,” *Lupus* (2007) 16, 401-409. [↑](#footnote-ref-7)
8. Al Daabil M, Massarotti EM, Fine A, Tsao H, Ho P, Schur PH, Bermas BL, Costenbader KH. Development of SLE among "potential SLE" patients seen in consultation: long-term follow-up. Int J Clin Pract. 2014 Dec;68(12):1508-13. [↑](#footnote-ref-8)
9. Rúa-Figueroa Í, Richi P, López-Longo FJ, Galindo M, Calvo-Alén J, Olivé-Marqués A, Loza-Santamaría E, Vicente SP, Erausquin C, Tomero E, Horcada L, Uriarte E, Sánchez-Atrio A, Rosas J, Montilla C, Fernández-Nebro A, Rodríguez-Gómez M, Vela P, Blanco R, Freire M, Silva L, Díez-Álvarez E, Ibáñez-Barceló M, Zea A, Narváez J, Martínez-Taboada V, Marenco JL, de Castro MF, Fernández-Berrizbeitia O, Hernández-Beriain JÁ, Gantes M, Hernández-Cruz B, Pérez-Venegas JJ, Pecondón Á, Marras C, Carreira P, Bonilla G, Torrente V, Castellví I, Alegre J, Moreno M, Raya E, de la Peña PG, Vázquez T, Aguirre Á, Quevedo V, Pego-Reigosa JM; EAS-SER (Systemic Diseases Study Group of the Spanish Society of Rheumatology). Comprehensive description of clinical characteristics of a large systemic lupus erythematosus cohort from the Spanish Rheumatology Society Lupus Registry (RELESSER) with emphasis on complete versus incomplete lupus differences. Medicine (Baltimore). 2015 Jan;94(1):e267. [↑](#footnote-ref-9)
10. Bourn, R., & James, J. A. (2015). Pre-clinical lupus. Current opinion in rheumatology, 27(5), 433. [↑](#footnote-ref-10)
11. Adamichou C, *et al*. *Ann Rheum Dis* 2021;**80**:758–766. doi:10.1136/annrheumdis-2020-219069 [↑](#footnote-ref-11)
12. Batu ED, Kaya Akca U, Basaran O, et al. Correspondence on ‘Lupus or not? SLE Risk Probability Index (SLERPI): a simple, clinician-friendly machine-learning-based model to assist the diagnosis of systemic lupus erythematosus.’ Ann Rheum Dis (2021). [↑](#footnote-ref-12)
13. Feinstein, A.R. “Clinical Judgment” revisited: the distraction of quantitative models. *Ann.*

 *Intern. Med.,* **120**, 799-805 (1994). [↑](#footnote-ref-13)
14. Feinstein, A.R., & Horwitz, R.I. Problems in the “Evidence” of “Evidence-Based Medicine.” *Am. J.*

 *Med.* **103**, 529-535 (1997) [↑](#footnote-ref-14)
15. Dinse GE, Parks CG, Weinberg CR, Co CA, Wilkerson J, Zeldin DC, Chan EKL, Miller FW. 2020. Increasing prevalence of antinuclear antibodies in the United States. Arthritis Rheum; doi: 10.1002/art.41214 [Online 8 April 2020].  [↑](#footnote-ref-15)
16. Berk, M., Williams, L.J., Jacka, F.N. *et al.* So depression is an inflammatory disease, but where does the inflammation come from?. *BMC Med* **11,**200 (2013). <https://doi.org/10.1186/1741-7015-11-200>; Jacka, F.N., O’Neil, A., Opie, R. et al. A randomised controlled trial of dietary improvement for adults with major depression (the ‘SMILES’ trial). BMC Med 15, 23 (2017). <https://doi.org/10.1186/s12916-017-0791-y> ; Parletta N, Zarnowiecki D, Cho J, Wilson A, Bogomolova S, Villani A, Itsiopoulos C, Niyonsenga T, Blunden S, Meyer B, Segal L, Baune BT, O'Dea K. A Mediterranean-style dietary intervention supplemented with fish oil improves diet quality and mental health in people with depression: A randomized controlled trial (HELFIMED). Nutr Neurosci. 2019 Jul;22(7):474-487. doi: 10.1080/1028415X.2017.1411320. Epub 2017 Dec 7. PMID: 29215971. [↑](#footnote-ref-16)
17. Constantin, M., Nita, I. E., Olteanu, R., Constantin, T., Bucur, S., Matei, C., Raducan, A."Significance and impact of dietary factors on systemic lupus erythematosus pathogenesis (Review)". Experimental and Therapeutic Medicine 17.2 (2019): 1085-1090. [↑](#footnote-ref-17)
18. Leiba A, Amital H, Gershwin ME, Shoenfeld Y. Diet and lupus. Lupus. 2001;10(3):246-8. doi: 10.1191/096120301674681790. PMID: 11315362. [↑](#footnote-ref-18)
19. Mu, Q., Zhang, H., Liao, X. *et al.* Control of lupus nephritis by changes of gut microbiota. *Microbiome* **5,**73 (2017). https://doi.org/10.1186/s40168-017-0300-8 [↑](#footnote-ref-19)
20. Klack K, Bonfa E, Borba Neto EF. Diet and nutritional aspects in systemic lupus erythematosus. Rev Bras Reumatol. 2012 May-Jun;52(3):384-408. English, Portuguese. PMID: 22641593. [↑](#footnote-ref-20)
21. Liu Y, Yu Y, Matarese G, La Cava A. Fasting-induced hypoleptinemia expands functional regulatory T cells in systemic lupus erythematosus. J Immunol. 2012 Mar 1;188(5):2070-3. doi: 10.4049/jimmunol.1102835. Epub 2012 Jan 30. PMID: 22291185; PMCID: PMC3288569. [↑](#footnote-ref-21)
22. Correa-Rodríguez M, Pocovi-Gerardino G, Callejas-Rubio JL, Ríos Fernández R, Martín-Amada M, Cruz-Caparros MG, Medina-Martínez I, Ortego-Centeno N, Rueda-Medina B. Dietary Intake of Free Sugars is Associated with Disease Activity and Dyslipidemia in Systemic Lupus Erythematosus Patients. Nutrients. 2020 Apr 15;12(4):1094. doi: 10.3390/nu12041094. PMID: 32326626; PMCID: PMC7231002. [↑](#footnote-ref-22)
23. Zerbo, O., Qian, Y., Yoshida, C. *et al.* Maternal Infection During Pregnancy and Autism Spectrum Disorders. *J Autism Dev Disord* **45,**4015–4025 (2015). <https://doi.org/10.1007/s10803-013-2016-3>

LH Lumey, Aryeh D Stein, Henry S Kahn, Karin M van der Pal-de Bruin, GJ Blauw, Patricia A Zybert, Ezra S Susser, Cohort Profile: The Dutch Hunger Winter Families Study, International Journal of Epidemiology, Volume 36, Issue 6, December 2007, Pages 1196–1204, https://doi.org/10.1093/ije/dym126 [↑](#footnote-ref-23)
24. Zhu, Z., Tang, S., Deng, X., & Wang, Y. “Maternal Systemic Lupus Erythematosus, Rheumatoid Arthritis, and Risk for Autism Spectrum Disorders in Offspring: A Meta‑analysis.” *Journal of Autism and Developmental Disorders* (2020) 50:2852–2859 <https://doi.org/10.1007/s10803-020-04400-y> [↑](#footnote-ref-24)
25. Kolata, G. “Grant System Leads Cancer Researchers to Play It Safe,” *New York Times,* June 28, 2009. [↑](#footnote-ref-25)