

Are Antinuclear Antibodies Always Pathological? Insights from Population Data

Bogdan Penev^{1*} 

1. Rheumatology Department, Sofamed University Hospital, Sofia, Bulgaria

* Correspondence:

Bogdan Penev, MD, PhD

Rheumatology Department, Sofamed University Hospital
Sofia, Bulgaria

Email: bogdanfpenev@gmail.com

ORCID: 0000-0001-5005-4259

Running title: Are ANAs Always Pathological?

Abstract

The testing of antinuclear antibodies (ANA) has become more frequent in routine clinical practice and the interpretation of positive results may pose a significant challenge. The objective of this study is to evaluate the current evidence on the prevalence of ANA in the general population and to discuss the clinical significance of ANA positivity in the absence of autoimmune rheumatic disease (ARD). A literature search was conducted using the PubMed database for articles investigating antinuclear antibodies in the general population published between 2015 and 2025. The analysis focused on large-scale population studies evaluating ANA positivity via indirect immunofluorescence (IIF) on HEp-2 cells, as well as research regarding ANA positivity of non-rheumatic origin. Furthermore, the immunological profile of ANA-positive healthy individuals is discussed. Recent data indicate an ANA prevalence ranging from 10% to 30% in the general population, significantly exceeding the estimated 2% prevalence of ARD. Studies from the US even demonstrate an increasing trend in ANA positivity over time. Immunologically, ANA-positive healthy individuals seem to exhibit a balanced, low-grade but persistent autoreactivity. Large phenome study data confirm strong associations with autoimmune diseases, Raynaud's syndrome, and alveolar fibrosing conditions, while revealing negative associations with certain non-autoimmune conditions like type 2

Received: May 1st, 2026
Accepted: May 31st 2026
Published: Jun 30th 2026
Copyright: © 2026 by the authors.
License: Bulgarian Society for Rheumatology.
This is an open access article distributed under the terms of the Creative Commons Attribution (CC BY) license.



diabetes and viral hepatitis C. ANA positivity in healthy individuals may represent a persistent benign autoreactivity rather than an impending disease. Thus ANA testing without clinical suspicion of ARD is often uninformative, and may cause unnecessary patient anxiety. More studies in adherence to international guidelines (EFLM/EASI/ICAP) and the use of standardized cutoff titers (preferably $\geq 1:160$ for pathology) as well as investigating the pathoimmunological basis of ANA-positive healthy individuals are warranted.

Keywords: Antinuclear antibodies, ANA prevalence, general population, autoimmune rheumatic diseases, indirect immunofluorescence, autoreactivity.

1. Introduction

Antinuclear antibodies (ANA) are perhaps the most frequently evaluated immunological marker in daily rheumatological practice, second only to rheumatoid factor and anti-citrullinated protein antibodies. Furthermore, as awareness of rheumatic diseases grows, ANA testing is increasingly ordered by non-rheumatologists. This has led to an accumulation of experience with the test, but also to questions regarding the interpretation of abnormal results in the absence of a clinical constellation for the specific diseases that manifest with ANA positivity [1].

In this brief review, we will address the current prevalence of ANA in the general population (GP) and discuss potential reasons for ANA positivity in the absence of an autoimmune rheumatic disease (ARD).

2. Materials and Methods

To assess the current prevalence of ANAs, we searched the PubMed database for articles published between 2015 and 2025, using the keywords "antinuclear antibodies" and "general population" in the title or abstract. This search was supplemented using the medical AI engine OpenEvidence to identify contemporary studies on ANA prevalence in the general population. The PubMed query yielded 25 articles; following a title and abstract review, three were selected [2-4], which were also identified by OpenEvidence. To better characterize the immunological profile of ANA-positive healthy individuals, we included a key 2020 study [5]. Furthermore, we discuss several large-scale studies examining ANA positivity independent of ARD. This review focuses on ANA screening via indirect immunofluorescence (IIF) on HEp-2 cells, the current gold standard [6]. According to the International Consensus on ANA Patterns

(ICAP), the term "ANA" also encompasses antibodies targeting extranuclear antigens, with a classification system comprising 17 nuclear, 9 cytoplasmic, and 5 mitotic staining patterns [6].

3. ANA in the General Population

3.1. Study Cohorts and Methodologies

The three selected population-based studies [2-4] investigate the prevalence of antinuclear antibodies (ANA) using indirect immunofluorescence (IIF). The first study, conducted across 18 cities in Germany, included 1,199 individuals [2]. The second took place across major administrative regions in Poland and comprised 1,731 individuals: 649 were clinically healthy, while 1,082 had an underlying disease [3]. Notably, the third study utilized the National Health and Nutrition Examination Survey (NHANES) registry and biobank. This longitudinal study analyzed sera and clinical data from over 13,000 individuals across three distinct time periods: 1988–1991, 1999–2004, and 2011–2012 [4]. To ensure consistency across these periods, all sera were processed in a single laboratory, relying on the proven long-term stability of antibodies stored at -80°C [7]. Furthermore, all three studies evaluated potential associations between ANA positivity and various collected health-related parameters.

3.2. Prevalence and Titer Thresholds

ANA assessment across the studies utilized multiple cutoff titers, ranging from 1:80 up to 1:1280, though non-standard titers, such as 1:100, were occasionally employed. Despite differences in threshold definitions, the overall ANA positivity rates ranged between 10% and 30%, demonstrating an inverse relationship between titer level and prevalence. Interestingly, the German and Polish cohorts yielded high positivity rates (20% to 30%) at low titers, whereas the longitudinal NHANES study reported a maximum prevalence of 10% to 16%. Furthermore, the NHANES data revealed a striking and significant increase in ANA positivity during the most recent study period compared to the two previous intervals (Fig. 1).

3.3 IIF Patterns

Regarding IIF patterns, the three studies are not directly comparable. The longitudinal NHANES study does not report on IIF patterns, and while the German study details these patterns, it does not utilize the ICAP nomenclature. In the German cohort, the speckled pattern was the most common (approximately 74%), followed by homogeneous (19%). Conversely, the Polish study utilized ICAP classifications, identifying AC-2

(dense fine speckled) as the most frequent pattern (50%), followed by AC-21 (cytoplasmic reticular/AMA-like; 15.4%), and the mixed AC-4/AC-5 pattern (fine/coarse speckled; 14.6%).

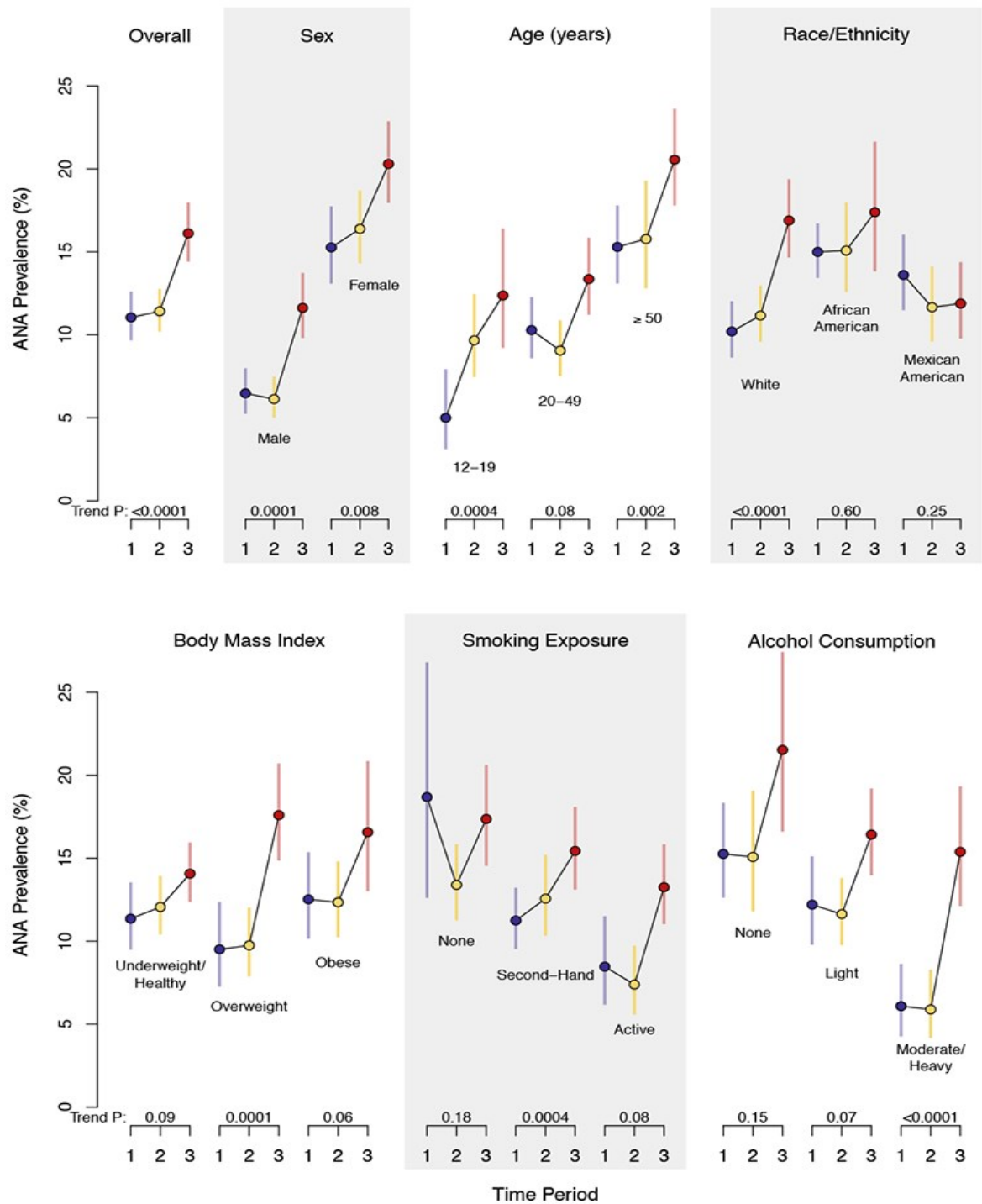


Figure 1. Trend of increasing ANA positivity (at 1:80) over a 25-year period, compared with variables included in the analysis. The trend is evident in all subgroups except for the Hispanic/Latino ethnicity group. Reproduced with permission from Dinse et al., Arthritis & Rheumatology, © 2022 American College of Rheumatology [3].

3.4 Demographic Associations: Age and Sex

The well-established age and sex distributions of ANA positivity are consistently reflected across all three studies. Regarding sex, ANA prevalence in women was up to three times higher than in men. In the Polish study, age-related analyses demonstrated the lowest ANA prevalence in individuals under 30 years of age (7.9%), with peaks occurring in the 60–70 years (20.6%) and >70 years (22.4%) cohorts; the other two studies yielded similar demographic trends. Additionally, while the longitudinal NHANES study observed significant increases in ANA positivity across all age categories over time, the most pronounced rise occurred among adolescents (12–19 years).

3.5 Cardiometabolic Risk Factors

As population-based registry studies, all three investigations analyzed the distribution of ANA in relation to traditional risk factors - such as obesity, hypertension, diabetes, and unhealthy lifestyle behaviors - finding no significant associations, or only modest ones. Notably, statistical modeling in the NHANES follow-up demonstrated that the temporal increase in ANA prevalence could not be attributed to rising population body mass index (BMI), despite a modest association, or increased alcohol consumption.

These findings are consistent with data reported prior to 2015. For instance, Satoh et al. [8] identified an ANA prevalence of approximately 15% (at a 1:80 titer) in the general population. Similar values have been corroborated by other studies [9, 10], demonstrating consistent results across various testing methodologies.

4. Immunological Profile of ANA-positive Healthy Individuals

Slight-Webb et al. [5] identified a 7% prevalence of ANA positivity among 790 healthy individuals, defined by the presence of at least one of 11 specific autoantibodies (including dsDNA, Ro/SSA, and Sm). Their analysis revealed a stepwise increase in pro-inflammatory cytokines - specifically IFN- γ , TNF, IL-17, and G-CSF - across the spectrum from ANA-negative to ANA-positive healthy subjects, peaking in patients with systemic lupus erythematosus (SLE). Notably, upstream mediators such as IFN- α , IFN- β , and IL-12p40 were elevated exclusively in the SLE cohort, while the regulatory IL-1Ra was significantly diminished.

Cellularly, ANA-positive healthy individuals exhibited increased frequencies of monocytes, memory B cells, and plasmablasts, alongside

enhanced pSTAT-3 and pSTAT-5 signaling. These data suggest that low-grade autoreactivity in healthy individuals is effectively sequestered by regulatory mechanisms, such as a high IL-1Ra/IL-1 β ratio and normal type 1 IFN levels. Similar immunological signatures have been observed in asymptomatic relatives of SLE patients [11]. It is important to note that the "ANA positivity" in the Slight-Webb study was defined by specific antibody assays rather than indirect immunofluorescence (IIF) patterns.

5. ANA in Non-Autoimmune Conditions

Cumulative evidence and clinical practice demonstrate a significant disparity between the prevalence of ANA positivity and the actual incidence of autoimmune rheumatic diseases. While the overall prevalence of ARDs is estimated at approximately 2% [12, 13], the broader spectrum of autoimmune diseases (AIDs) - including autoimmune thyroid and liver diseases - appear to affect roughly 10.2% of the population in some studies [14].

Beyond established AIDs, elevated ANA titers are traditionally attributed to conditions involving extensive cell destruction and the subsequent externalization of nuclear antigens, such as malignancies, chronic infections, and, less frequently, drug-induced triggers [15, 16]. Furthermore, a positive ANA may represent a preclinical stage, preceding the symptomatic onset of an ARD by several years [17]. However, even after accounting for preclinical cases and known comorbidities, the high frequency of ANA positivity in large-scale epidemiological cohorts remains partially unexplained [18]. This suggests that ANA prevalence exceeds the "presumed" patient population, raising questions about its association with non-rheumatic and non-autoimmune factors. The following sections review the evidence regarding these alternative associations.

5.1 The Zanussi et al. Study: A Phenome-Wide Perspective

A methodologically robust, large-scale study by Zanussi et al. [19] utilized the electronic health records of the Vanderbilt University Medical Center to conduct a Phenome-Wide Association Study (PheWAS)*. Analyzing a cohort of 70,043 individuals tested between 2000 and 2019, the authors defined ANA positivity as a titer $\geq 1:80$ on HEp-2 cells. Of the total cohort, 26,579 (38%) were ANA-positive. Notably, ANA positivity was found in 53.3% of patients with a known autoimmune disease (AID) and in 31.7% of those without an AID.

When analyzing the entire cohort, systemic connective tissue diseases (CTDs) and rheumatoid arthritis-related conditions showed the strongest associations with ANA positivity (Odds Ratio, OR > 3, reaching up to 11), followed by nephritis. Intriguingly, the study also identified significant inverse associations (OR < 1.0, ranging down to 0.8) between ANA positivity and several non-autoimmune conditions, including hepatitis C, arterial hypertension, type 2 diabetes, convulsive disorders, mood disorders, and substance abuse (smoking and alcohol), as shown in Fig. 2A.

The authors further stratified the analysis into two subcohorts: 1) Patients with AID: The associations largely mirrored those of the general cohort across 136 diseases; 2) Patients without AID: In this group, 13 diagnoses remained significantly associated with ANA positivity (Fig. 2B), most notably Raynaud's syndrome (OR 2.1), idiopathic pulmonary fibrosis (OR 1.5), alveolar pneumopathies (OR 1.4), and arthrosis (OR 1.3). Conversely, negative associations persisted for viral hepatitis C, febrile conditions, and tobacco/alcohol use.

Ultimately, the study concluded that while ANA are primarily biomarkers for autoimmune and interstitial lung conditions, they do not show an association with neoplastic or cardiovascular diseases. The authors noted several limitations: the cohort was not representative of the general population (consisting of clinically indicated tests), the study was conducted at a tertiary care center, and the potential confounding effect of medications was not analyzed.

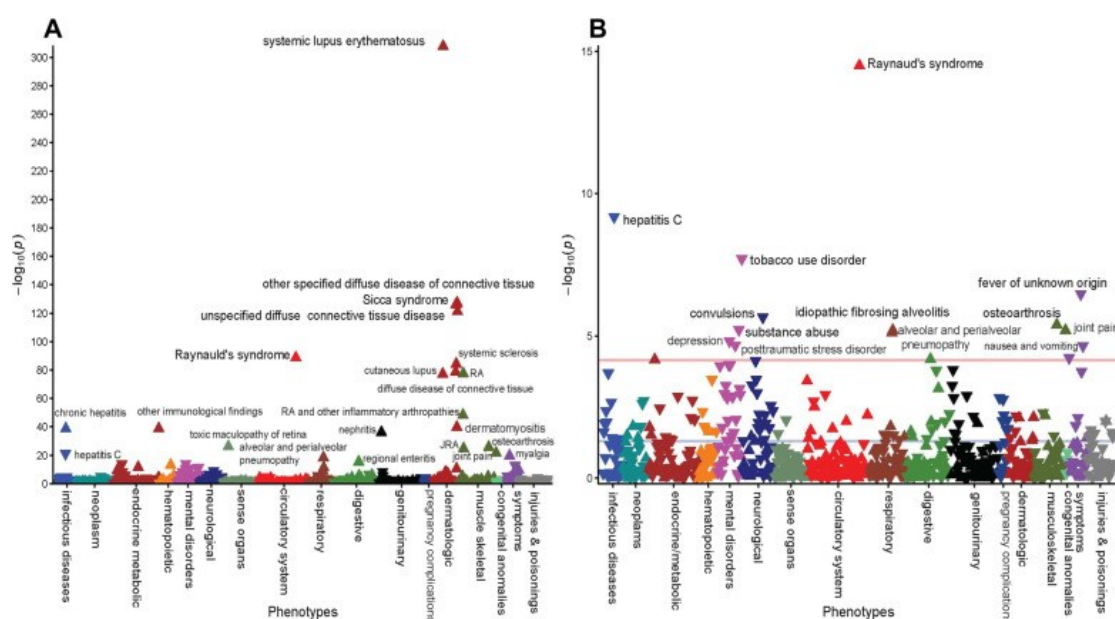


Figure 2. Clinical diagnoses associated with ANA (titer $\geq 1:80$) in (A) all tested individuals and (B) individuals without autoimmune diseases. $\blacktriangle$ and $\blacktriangledown$ denote increased ($OR > 1$) and decreased ($OR < 1$) risk, respectively. The red horizontal

line represents $P \leq 5 \times 10^{-5}$. The twenty-two diagnoses with the most significant P-value associations out of the 88 significant associations are labeled in the entire cohort (A), and all 13 significant associations are labeled in those without autoimmune disease (B). Reproduced from Zanussi et al. (2023), Clinical diagnoses associated with a positive antinuclear antibody test in patients with and without autoimmune disease, BMC Rheumatology, under the terms of the Creative Commons Attribution 4.0 International License.

5.2 High Titers and Hepatic Complications

Building upon the Vanderbilt database and PheWAS methodology, Chung et al. (2025) [20] investigated 28,781 individuals without known AIDs, stratifying them by ANA titer: high ($\geq 1:640$), low ($\geq 1:80$), and negative. Their analysis revealed a robust association between high-titer ANA and liver disease, including severe complications such as portal hypertension and ascites, underscoring the clinical relevance of titer magnitude even in the absence of overt autoimmunity.

5.3 Cardiovascular Risk and All-Cause Mortality

Given the established link between subclinical inflammation and cardiovascular disease, Solow et al. [21] investigated the association between ANA positivity and cardiovascular risk factors in a cohort of 3,488 individuals. They found no significant correlation with traditional markers such as high-sensitivity C-reactive protein, aortic intimal thickness, or vascular calcium scores. However, they did identify subtle markers of endothelial and immune dysregulation among ANA-positive subjects.

Conversely, utilizing the large-scale NHANES registry, Dinse et al. [22] followed 3,357 individuals longitudinally and reported a significant, albeit modest, association between ANA positivity ($\geq 1:80$) and all-cause mortality. Specifically, elevated mortality risks were observed for cardiovascular diseases (Hazard Ratio, HR 1.60) and malignancies (HR 1.58).

5.4 Drug-Induced ANA: Re-evaluating Traditional Risks

Medication-induced ANA and ARDs are well-documented clinical phenomena (e.g., with hydralazine or carbamazepine). To evaluate this at a population level, Dinse's group [23] utilized the NHANES registry to assess associations between ANA positivity and prescribed therapeutics. Surprisingly, they found no positive associations with medications traditionally deemed high-risk. Instead, significant associations emerged with loop diuretics across all age groups, and with bronchodilators and benzodiazepines specifically in older adults. A particularly intriguing finding was the age-dependent effect of estrogen therapy: it was positively

associated with ANA in older women (OR 1.80) but demonstrated an inverse association in younger women aged 18–59 (OR 0.43).

5.5 ANA Patterns and Malignancy Risk

Finally, the complex relationship between ANA and neoplasms was highlighted in a recent cohort study of 15,728 oncology patients [24]. The authors demonstrated that the indirect immunofluorescence (IIF) staining pattern may hold prognostic value: the nucleolar pattern was associated with an increased risk of malignancy, whereas homogeneous and speckled patterns correlated with a reduced risk. While statistically significant, the associations were modest, with relative risks (RR) ranging between 1.2 and 1.5.

6. Discussion

The evidence synthesized in this review confirms the presence of a substantial percentage of ANA-positive individuals within the general population. However, determining the exact magnitude of this prevalence remains challenging, as studies - both pre- and post-2015 - frequently employ different methodologies and cutoff values, precluding direct comparison and broad generalization. Although indirect immunofluorescence (IIF) has increasingly become the gold standard in post-2015 research, comparable cutoff titers are still not universally applied. Furthermore, since 2014, an increasing number of countries have adopted a titer of 1:160 as the upper limit of normal [25], which contrasts with the 1:80 threshold utilized as an entry criterion for systemic lupus erythematosus (SLE) since 2019 [26]. Even when assuming a 1:160 cutoff, recent data still demonstrate a wide prevalence range, from 10% to approximately 30% in post-2015 cohorts, compared to the 2.5% to 10% range reported in earlier large-scale studies [8, 9]. Within this context, the US-based study highlighting the increasing prevalence of ANA is particularly notable. While methodologically robust, its findings cannot be directly extrapolated to European or global populations, despite largely excluding confounding factors such as obesity and alcohol consumption. Nevertheless, the study corroborates that female sex and advancing age are significant factors contributing to elevated ANA titers.

These discrepancies naturally raise questions regarding the definition of clinical normality, given that reference limits for biological markers are traditionally defined by the values encompassing 95% of a healthy reference population [27]. Addressing this, the joint recommendations of the EFLM/EASI/ICAP** [28] suggest that while screening should be

initiated at 1:80 due to its high sensitivity, specificity increases significantly at $\geq 1:160$, making the latter the more appropriate threshold for defining pathology. These guidelines are largely supported by a major Indian study [29] comparing titers between healthy individuals and those with major connective tissue diseases, as well as by the previously described Polish cohort [3].

As highlighted throughout this review, the prevalence of ANA in the general population significantly exceeds the estimated number of "expected" ANA-positive individuals - namely, those with an autoimmune rheumatic disease, other autoimmune diseases, or known non-autoimmune conditions associated with ANA formation. This raises a fundamental question regarding the origin and clinical significance of elevated ANA in clinically healthy individuals or patients with unrelated pathologies. Given that ANA formation implies an underlying immunological perturbation, as delineated by Slight-Webb et al. [5], it is plausible to hypothesize that these represent partial disruptions in immunological homeostasis that are prevalent across the general population. For the vast majority, these disruptions remain fully compensated and do not progress to clinical disease. However, they do persist over time, as evidenced by data showing that elevated ANAs often remain stable longitudinally [30]. This phenomenon is particularly pronounced among relatives of SLE patients, who exhibit a much higher frequency of ANA positivity compared to the general population - a finding supported by our own previous investigations [31]. Ultimately, ANA positivity in "healthy" individuals can be viewed not merely as a false positive, but rather as an indicator of persistent, benign autoreactivity.

7. Messages for Clinical and Scientific Practice

The reviewed studies indicate that while ANAs are predominantly associated with autoimmune diseases - particularly rheumatic conditions - they also exhibit weaker associations with a heterogeneous group of disorders for which ANA testing is not currently diagnostic. Furthermore, a substantial cohort of ANA-positive healthy individuals remains, for whom the presence of these autoantibodies cannot be readily explained by overt pathology.

Consequently, we maintain that conducting ANA testing via IIF in the absence of clinical suspicion for an autoimmune rheumatic disease (ARD) is uninformative. Such indiscriminate screening frequently triggers a cascade of extensive and costly diagnostic workups that rarely yield decisive clinical outcomes. This aligns with the American College of Rheumatology's

"Choosing Wisely" recommendation, which explicitly states not to "test ANA in patients without specific symptoms (e.g., photosensitivity, malar rash, symmetric polyarthritis, etc.) because a positive ANA test does not confirm a diagnosis in the absence of clinical symptoms" [1]. Importantly, an incidental positive result can cause significant, long-lasting patient anxiety, especially given the tendency for elevated ANA titers to persist over time. Conversely, when clinical suspicion of an ARD - particularly a systemic connective tissue disease - is present, IIF ANA testing, complete with the identification of the ICAP staining pattern, remains a vital tool for guiding subsequent investigations.

From a research perspective, future ANA studies should strictly adhere to the joint EFLM/EASI/ICAP recommendations [28]. Utilizing standardized reference dilutions (1:80 for screening and 1:160 for pathology) and uniformly reporting ICAP staining patterns will ensure methodological consistency and comparability across cohorts. Finally, a significant gap in the current literature remains: there is a lack of comprehensive research investigating the underlying immunological profile - both cytokine and cellular - of clinically healthy individuals who exhibit IIF-ANA positivity but test negative for isolated specific autoantibodies.

8. Conclusions

Recent population-level studies indicate that the prevalence of ANA positivity - defined by elevated titers on IIF using HEp-2 cells - is greater than 10%. This proportion significantly outweighs the combined prevalence of established ARDs, incipient ARDs, and other non-rheumatic conditions associated with elevated ANA. Additionally, current evidence suggests that ANA positivity in healthy individuals arises from gradual shifts in immune homeostasis that fail to breach immunological tolerance due to preserved regulatory mechanisms. Ultimately, these observations imply that ANA positivity in the general population is largely driven by a widespread, benign autoreactivity rather than an occult, serious underlying condition.

** The term phenome is derived from phenotype, analogous to genome from genotype. While genomic studies (e.g., GWAS) typically start with a specific disease and scan the genome for associated genetic variants, phenomic studies (PheWAS) apply an inverse approach: they start with a specific marker or trait (such as ANA positivity) and scan the "phenome" (a comprehensive array of clinical diagnoses) to identify novel associations. In the referenced study, the cohort was stratified by the presence or absence of*

an autoimmune disease (AID), and the authors systematically screened for broader clinical phenotypes associated with ANA positivity.

*** EFLM/EASI/ICAP: European Federation of Clinical Chemistry and Laboratory Medicine (EFLM), European Autoimmune Standardization Initiative (EASI), and International Consensus on Antinuclear Antibody Patterns (ICAP).*

Declarations

Author Contributions

Conceptualization: B.P; Methodology: B.P; Formal analysis: B.P; Investigation: B.P; Writing—original draft: B.P; Writing—review & editing: B.P. During the preparation of this work, the author used Gemini to translate portions of the original text from Bulgarian to English and to improve the overall language and readability of the manuscript. Additionally, generative AI was used to draft the initial version of the abstract. For the literature review process, the medical AI platform OpenEvidence was utilized to supplement the search for relevant articles, as detailed in the Methods section. After using these tools, the author carefully reviewed, edited, and verified all content, and takes full responsibility for the accuracy, originality, and final content of the publication.

Funding

This research received no external funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Akmatov MK, Römer M, Mikolajczyk RT et al. Anti-nuclear autoantibodies in the general German population: prevalence and lack of association with selected cardiovascular and metabolic disorders-findings of a multicenter population-based study. *Arthritis Res Ther*. 2017 Jun 6;19(1):127. doi: 10.1186/s13075-017-1338-5.
2. Krzemień P, Kasperczyk J, Banach M, et al. Analysis of the impact of sex and age on the variation in the prevalence of antinuclear autoantibodies in Polish population: a nationwide observational, cross-sectional study. *Rheumatol Int.*, 2022 Feb;42(2):261-271. doi: 10.1007/s00296-021-05033-9.
3. Dinse GE, Parks CG, Weinberg CR, et al. Increasing Prevalence of Antinuclear Antibodies in the United States. *Arthritis Rheumatol.*, 2022 Dec;74(12):2032-2041. doi: 10.1002/art.42330.
4. Slight-Webb S, Smith M, Bylinska A, et al. Autoantibody-positive healthy individuals with lower lupus risk display a unique immune endotype. *Journal Of Allergy And Clinical Immunology*, (2020)146(6), 1419-1433. <https://doi.org/10.1016/j.jaci.2020.04.047>
5. Damoiseaux J, Andrade LE, Carballo OG, et al. Clinical relevance of HEp-2 indirect immunofluorescent patterns: the International Consensus on ANA patterns (ICAP) perspective. *Ann Rheum Dis*. 2019;78:879-889. doi: 10.1136/annrheumdis-2018-214436.
6. Argentieri MC, Pilla D, Vanzati A, et al. Antibodies are forever: a study using 12-26-year-old expired antibodies. *Histopathology*. 2013;63(6):869-76.
7. Satoh M, Chan EK, Ho LA, et al. (2012) Prevalence and sociodemographic correlates of antinuclear antibodies in the United States. *Arthritis & Rheumatism*. 2012;64(7):2319-27. <https://doi.org/10.1002/art.34380>
8. Wandstrat A, Carrjohnson, F., Branch, V., et al. (2006). Autoantibody profiling to identify individuals at risk for systemic lupus erythematosus. *Journal Of Autoimmunity*, 27(3), 153-160. <https://doi.org/10.1016/j.jaut.2006.09.001>
9. Li X, Liu X, Cui J, et al. (2019) Epidemiological survey of antinuclear antibodies in healthy population and analysis of clinical characteristics of positive population. *Journal of Clinical Laboratory Analysis*. 2019;33(8). <https://doi.org/10.1002/jcla.22965>
10. Munroe, M., Young, K., Kamen, D, et al. (2017). Discerning Risk of Disease Transition in Relatives of Systemic Lupus Erythematosus Patients Utilizing Soluble Mediators and Clinical Features. *Arthritis & Rheumatology*, 69(3), 630-642. <https://doi.org/10.1002/art.40004>
11. Bournia VK, Fragoulis GE, Mitrou P, et al. Increased prevalence of inflammatory arthritis, systemic lupus erythematosus and systemic sclerosis, during 2020-2023 versus 2016-2019 in a Nation-Wide Cohort Study. *Rheumatol Int*. 2024 Dec;44(12):2837-2846. doi: 10.1007/s00296-024-05733-y.
12. Goldblatt F, O'Neill SG. Clinical aspects of autoimmune rheumatic diseases. *Lancet*. 2013 Aug 31;382(9894):797-808. doi: 10.1016/S0140-6736(13)61499-3.
13. Conrad N, Misra S, Verbakel JY, et al. Incidence, prevalence, and co-occurrence of autoimmune disorders over time and by age, sex, and socioeconomic status: a population-based cohort study of 22 million individuals in the UK. *Lancet*. 2023 Jun 3;401(10391):1878-1890. doi: 10.1016/S0140-6736(23)00457-9.

14. Im JH, Chung MH, Park YK, et al. Antinuclear antibodies in infectious diseases. *Infect Dis (Lond)*. 2020 Mar;52(3):177-185. doi: 10.1080/23744235.2019.1690676.
15. Vlăgea A, Falagan S, Gutiérrez-Gutiérrez G, et al. Antinuclear antibodies and cancer: A literature review. *Crit Rev Oncol Hematol*. 2018 Jul;127:42-49. doi: 10.1016/j.critrevonc.2018.05.002.
16. Arbuckle, M., McClain, M., Rubertone, M., Scofield, R., Dennis, G., James, J., & Harley, J. (2003). Development of Autoantibodies before the Clinical Onset of Systemic Lupus Erythematosus. *New England Journal Of Medicine*, 349(16), 1526-1533. <https://doi.org/10.1056/nejmoa021933>
17. Wandstrat, A., Carrjohnson, F., Branch, V., et al. (2006). Autoantibody profiling to identify individuals at risk for systemic lupus erythematosus. *Journal Of Autoimmunity*, 27(3), 153-160. <https://doi.org/10.1016/j.jaut.2006.09.001>
18. Zanussi JT, Zhao J, Wei WQ, et al. Clinical diagnoses associated with a positive antinuclear antibody test in patients with and without autoimmune disease. *BMC Rheumatol*. 2023 Aug 7;7(1):24. doi: 10.1186/s41927-023-00349-4.
19. Chung M, Shelley JP, Karakoc G, et al. Clinical conditions associated with a high antinuclear antibody titer in individuals without autoimmune disease. *Arthritis Care Res (Hoboken)*. 2025 Oct 15. doi: 10.1002/acr.25682.
20. Solow EB, Vongpatanasin W, Skaug B, et al. Antinuclear antibodies in the general population: positive association with inflammatory and vascular biomarkers but not traditional cardiovascular risk factors. *Clin Exp Rheumatol*. 2018 Nov-Dec;36(6):1031-1037.
21. Dinse GE, Parks CG, Weinberg CR, et al. Antinuclear antibodies and mortality in the National Health and Nutrition Examination Survey (1999-2004). *PLoS One*. 2017 Oct 9;12(10):e0185977. doi: 10.1371/journal.pone.0185977.
22. Dinse GE, Parks CG, Meier HCS, et al. Prescription medication use and antinuclear antibodies in the United States, 1999-2004. *J Autoimmun*. 2018 Aug;92:93-103. doi: 10.1016/j.jaut.2018.05.006.
23. Gauderon A, Roux-Lombard P, Spoerl D. Antinuclear Antibodies With a Homogeneous and Speckled Immunofluorescence Pattern Are Associated With Lack of Cancer While Those With a Nucleolar Pattern With the Presence of Cancer. *Front Med (Lausanne)*. 2020 Apr 30;7:165. doi: 10.3389/fmed.2020.00165.
24. Agmon-Levin N, Damoiseaux J, Kallenberg C, et al. International recommendations for the assessment of autoantibodies to cellular antigens referred to as anti-nuclear antibodies. *Ann Rheum Dis*. 2014 Jan;73(1):17-23. doi: 10.1136/annrheumdis-2013-203863.
25. Aringer M, Costenbader K et al., 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. *Arthritis Rheumatol*. 2019 Sep;71(9):1400-1412. doi: 10.1002/art.40930.
26. Ozarda Y, Sikaris K, Streichert T, Macri J; IFCC Committee on Reference intervals and Decision Limits (C-RIDL). Distinguishing reference intervals and clinical decision limits - A review by the IFCC Committee on Reference Intervals and Decision Limits. *Crit Rev Clin Lab Sci*. 2018 Sep;55(6):420-431. doi: 10.1080/10408363.2018.1482256.
27. Bonroy C et al., European Federation of Laboratory Medicine (EFLM) Working Group "Autoimmunity Testing," the European Autoimmune Standardization Initiative (EASI) and International Consensus on Antinuclear Antibody Patterns (ICAP). Detection of

- antinuclear antibodies: recommendations from EFLM, EASI and ICAP. *Clin Chem Lab Med*. 2023 Mar 29;61(7):1167-1198. doi: 10.1515/cclm-2023-0209.
28. Ghosh P, Dwivedi S, Naik S, et al. Antinuclear antibodies by indirect immunofluorescence : optimum screening dilution for diagnosis of systemic lupus erythematosus. *Indian J Med Res*. 2007 Jul;126(1):34-8.
29. Yeo AL, Le S, Ong J, et al. Utility of repeated antinuclear antibody tests: a retrospective database study. *Lancet Rheumatol*. 2020 Jul;2(7):e412-e417. doi: 10.1016/S2665-9913(20)30084-9.
30. Penev B, Vasilev G, Todorova EI, et al. First-degree relatives of patients with systemic lupus erythematosus: Autoreactivity but not autoimmunity? *Int J Rheum Dis*. 2023 May;26(5):907-916. doi: 10.1111/1756-185X.14669.
31. American College of Rheumatology. Five Things Physicians and Patients Should Question. Choosing Wisely: An initiative of the ABIM Foundation; 2013. Available from: <https://www.choosingwisely.org/societies/american-college-of-rheumatology/>

Винаги ли са патологични антинуклеарните антитела? Изводи от популационни данни

Резюме

Изследването на антинуклеарни антитела (АНА) става все по-често в рутинната клинична практика, а интерпретацията на положителните резултати може да представлява значително предизвикателство. Целта на този доклад е да се оценят съвременните данни за разпространението на АНА в общата популация и да се обсъди клиничното значение на АНА-позитивността при липса на автоимунно ревматично заболяване (АРЗ). Проведен е литературен обзор в базата данни PubMed за статии, изследващи антинуклеарните антитела (АНА) сред общата популация, публикувани в периода 2015–2025 г. Търсенето е с фокус върху мащабни популационни проучвания, оценяващи АНА-позитивността по метода на индиректна имунофлуоресценция (ИИФ) върху HEp-2 клетки, както и върху изследвания, засягащи АНА-позитивност с неревматичен произход. В допълнение е разгледан имунологичният профил на АНА-позитивни здрави индивиди. Съвременните данни показват разпространение на АНА-позитивност в общата популация между 10% и 30%, което значително надвишава очакваната честота на АРЗ от приблизително 2%. Проучвания от САЩ дори демонстрират тенденция към нарастване на АНА-позитивността във времето. От имунологична гледна точка АНА-позитивните здрави индивиди изглежда проявяват балансирана, лекостепенна, но персистираща автореактивност. Данни от мащабно феномно изследване потвърждава силни асоциации с автоимунни заболявания, синдром на Рейно и алвеоларни фиброзиращи състояния, като същевременно разкрива отрицателни асоциации с определени неавтоимунни състояния, като захарен диабет тип 2 и вирусен хепатит С. АНА-позитивността при здрави индивиди може да представлява персистираща бенигна автореактивност, а не предстоящо ревматично заболяване. Поради това изследването на АНА без клинично подозрение за АРЗ често е неинформативно и може да предизвика ненужна тревожност у пациента. Необходими са допълнителни проучвания в съответствие с международните насоки (EFLM/EASI/ICAP) и използването на стандартизирани прагови титри (за предпочитане $\geq 1:160$), както и изследване на патоимунологичната основа на АНА-позитивността при здрави индивиди.

Ключови думи: антинуклеарни антитела, разпространение на АНА, обща популация, автоимунни ревматични заболявания, индиректна имунофлуоресценция, автореактивност.