Society for Women's Health Research

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PolicyBrief

The Need for Diversity in Autoimmune Disease Research Trials

How Overlooking Diversity Hampers Knowledge and Impacts Outcomes

While it is known now that many factors, including biological factors, may contribute to differences in clinical outcomes in men and women, prior to the 1990s, women were excluded from clinical trials in the United States, and there was an overreliance on male mice in research studies. Over time, it was determined that the exclusion of women from clinical research was detrimental to their health.

In 1993, the U.S. Food and Drug Administration (FDA) rescinded a 1977 policy that excluded women of child-bearing age from clinical trials, and although the National Institutes of Health (NIH) has required that women and underrepresented minority populations be included in clinical trials since 1986, this policy was not given the force of law until the enactment of the NIH Revitalization Act in 1993. Further, it was not until 2016, with the implementation of the NIH Policy on Sex as a Biological Variable (SABV) that the NIH made clear its expectation that SABV should be factored into research designs, analyses, and reporting in vertebrate animal and human studies.

Still, the historical exclusion of women and underrepresented minority populations in research has had repercussions. While the United States has made progress to close these gaps, the decades of exclusion and underrepresentation has—in essence—left the nation playing "catch up" from underfunding and understudying diseases and conditions that disproportionately impact women, including autoimmune diseases and conditions.*

Tackling autoimmune diseases and conditions is dependent on understanding genetic and environmental mechanisms of disease and identifying treatments and interventions that apply for everyone, regardless of sex, gender, race, or ethnicity. Therefore, the exclusion of any population from related clinical trials limits our understanding of these diseases and leaves us ill-equipped to provide the safest and most effective treatments and interventions.

* *Note: Immune-mediated inflammatory diseases (IMIDs) are diseases where the causes and mechanisms of action are not fully understood, but a malfunction of the immune system is involved. Autoimmune diseases are a subset of IMIDs and are characterized by antigen presence. For the purposes of this document, "autoimmune diseases" refers to diseases and conditions across both classifications.*

KEY MESSAGES

- Research has shown that autoimmune diseases are more prevalent among females and may disproportionately impact specific racial groups. Yet, certain populations remain underrepresented in clinical trials.
- People respond differently to different types of medications and treatments. These varying responses can be caused by genetic differences, drug interactions, inflammation, and more. Therefore, ensuring that clinical trials include a diversity of patients is critical to reduce health disparities and advance health equity.
- Prior to the 1990s, women were excluded from clinical trials. This exclusion resulted in decades of untapped scientific opportunity and advancement. Science is now playing "catch-up" from lost years.
- The incidence of autoimmune disease is increasing globally, particularly in industrialized countries, such as the United States. Increasing investments in autoimmune clinical trials that represent the treatment population is a growing national imperative.

Issue Overview

Despite the prevalence of autoimmunity being on the rise in the United States, autoimmune diseases and conditions—and their impact on certain populations, including women—are not well understood. Research has indicated that a woman's environment, the gut microbiome, hormones, and sex chromosomes may play a role in why autoimmune diseases and conditions are more prevalent among women. However, a historical lack of research on autoimmune diseases in women and among subpopulations of women has affected our broader understanding of these diseases.

This is particularly problematic because women have a higher incidence and prevalence of autoimmune diseases than men; they represent 80 percent of the patients diagnosed with autoimmune diseases. Further, among women, there has been underrepresentation of certain populations of women in clinical trials. This includes racial and ethnic minority populations and pregnant and lactating populations. As a result, we have a narrower understanding of the underlying mechanisms of disease that may be unique to or different for women as well as of how certain drugs and therapies work in different populations.

Further, having homogenous populations in clinical trials results in an inability to provide personalized, evidence-based treatments and therapies for autoimmune patients. Currently, there is no cure for autoimmune diseases, so treatments often focus on managing symptoms. However, given the complexity of autoimmune diseases and conditions and their variability in patients, these treatments may fall short. As described in the 2020 *Cell* article, "Challenges, Progress, and Prospects of Developing Therapies to Treat Autoimmune Diseases":

"The complexity of autoimmune diseases has become increasingly clear, but current treatments are based on a simplistic and reductionist pathogenic understanding… All classes of drugs have in common that they are broadly acting, not disease specific, and associated with considerable side effects and, thus, impersonalized, in contrast to the more specific and personalized treatment that has already entered the oncology field. To achieve more specific and personalized treatment of patients with autoimmune diseases will require a more detailed understanding of the complexity of individual autoimmune diseases and how they unfold in individual patients."

"We're in the thick of sex and gender difference research from a basic level all the way to applying that research, in terms of translating clinical findings into care models and how we measure outcomes… What we're really missing is the fact that this is an approach and a lens through which it's critical to not only do science writ large but also one through which we need to look at drug research, toxicology research, and so forth. It's a critically important lens."

– Paula Johnson, MD, MPH, Chief, Division of Women's Health, Brigham and Women's Hospital, Interview, The Guardian

While progress has been made to improve diversity in research, the historical exclusion of certain populations has had lasting repercussions and has impacted health and quality of life as well as economic outcomes. Examples of this include the following:

- **Women's Representation in Rheumatoid Arthritis Research**. Rheumatoid arthritis (RA), an autoimmune disease that causes pain and joint inflammation, affects approximately 1.3 million adults in the United States and costs the economy over $40 billion each year. RA is more common among women than men (estimates project that women will account for more than 58% of all RA cases by 2040). According to research from the RAND Corporation, commissioned by Women's Health Access Matters (WHAM) for the report *Societal Impact of Research Funding for Women's Health in Rheumatoid Arthritis*, "Within the portfolio of extramural funding for RA research from the NIH over the past five fiscal

years, funding with a specific focus on women's health research accounted for 7 percent of total funding" and found that "few studies have employed models stratified by sex or gender to test the sex and gender differences of RA." Their analysis determined that investing $6 million in RA research focused on women would yield $10.5 billion in returns to the economy. Further, they determined that the investment in RA research focused on women would improve quality of life, add 32,000 years back to our workforce for patients and caregivers, and save $180 million in health care costs.

- **Pregnant and Lactating Populations in Research**. While pregnant and lactating populations have a long history of exclusion from clinical research, the exclusion of these populations from autoimmune clinical trials has implications for the ability to inform clinical care of those who are pregnant or wishing to become pregnant and could affect health outcomes for both mother and baby.

  As noted above, treatment for autoimmune disease centers on managing symptoms and slowing the progression of the disease. For some autoimmune diseases, delays in taking medication can result in greater disability and irreversible health losses. Yet, it is also known that autoimmune diseases and conditions can have pregnancy-associated changes. As shared by Doctors Kristina Waldorf and J. Lee Nelson in a 2009 *Immunological Investigations* article, "For women who have an autoimmune disease and subsequently become pregnant, pregnancy can induce amelioration of the mother's disease, such as in rheumatoid arthritis, while exacerbating or having no effect on other autoimmune diseases like systemic lupus erythematosus" (SLE).

  It is important for women and their health care providers to have evidence about the safety and efficacy of medications throughout their pregnancy in order to make the best decision for them and their families. More than 3.6 million women in the United States give birth each year, including those that are affected by illnesses that may require either ongoing or urgent treatment during pregnancy. According to the Centers for Disease Control and Prevention, about 9 in 10 women take at least one medicine during pregnancy, and 7 in 10 take at least one prescription medication.

> "The idea of an 'average patient' is difficult to define from an autoimmune disease standpoint as people's symptoms, severity, and response to treatment can all differ."
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> *– Molly Murray, President and CEO, Autoimmune Association, "Addressing the Needs of People Living with Autoimmune Disorders: A Conversation With Molly Murray," National Pharmaceutical Council (2022)*

  "Nonetheless," say the authors of a 2013 *Women's Health Issues* article "very few drugs are approved for use during pregnancy. In addition, most drug labels have little pregnancy data to inform prescribing decisions… Although there are significant physiologic changes in pregnancy, including near doubling of maternal blood volume and alterations in binding proteins, the pharmacokinetics and efficacy of drugs in pregnancy are, by and large, unknown… As a result, therapeutic decisions for pregnant women are often made without an evidence base. Treatment of the mother may be inadequate, exposing the fetus to therapies at a dose which does not provide a benefit to the mother."

- **Trial Population Not Representing the Treatment Population**. In a 2022 editorial in *ACR Open Rheumatology*, authors cited clinical trials for belimumab, which is a biologic treatment for SLE, as a case study for how clinical trials often do not sufficiently represent the populations for whom they are intended to serve, including racial and ethnic minorities. As noted in the piece, "SLE disproportionately affects individuals of Black African ancestry and of Hispanic/Latino ethnicity, who have greater morbidity and mortality from the disease."

  Due to both "patient- and provider-side barriers," the authors found that white patients, who constitute 33% of prevalent lupus cases, represented 51% of lupus clinical trial participants, whereas Black patients comprised only 14% of trial participants despite making up 43% of prevalent lupus cases. Research has shown that there are "significant differences among racial and ethnic groups in the metabolism, clinical effectiveness, and side effect profiles of many clinically important drugs." Therefore, ensuring these populations are adequately represented in clinical trials is vital for demonstrating drug safety and effectiveness among different populations.

Recommendations

Autoimmune diseases take a greater toll on women – particularly certain populations of women. Yet, these populations are not always sufficiently represented in research. In order to ensure that treatments, medications, and interventions work for everyone—and namely, the population whom they affect most—there must be diverse representation within clinical trials. This diversity could be improved through the implementation of policies that:

- Seek to improve the recruitment and retention of underrepresented and marginalized populations in clinical trials
- Critically assess clinical trial exclusion criteria to ensure that it will not inadvertently omit members of the treatment population for whom the intervention is intended to serve
- Create mechanisms—with input from key stakeholders—for internal and external accountability, including monitoring efforts to engage communities in clinical trials
- Provide education around the importance of participating in clinical trials
- Remove barriers to, or provide incentives for, participating in clinical trials