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Breaking research silos to achieve equitable precision medicine in rheumatology

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Abstract

Health disparities in rheumatic disease are well established and urgently need addressing. Obstacles to precision medicine equity span both the clinical and the research domains, with a focus placed on structural barriers limiting equitable health care access and inclusivity in research. Less articulated factors include the use of inaccurate population descriptors and the existence of research silos in rheumatology research, which creates a knowledge gap that precludes addressing the health disparities and fulfilling the goals of precision medicine to understand the ‘full patient’. The biopsychosocial model is a research framework that intertwines layers of biological and environmental effects to understand disease. However, very limited rheumatology research bridges across molecular and epidemiological studies of environmental exposures, such as physical and social determinants of health. In this Review, we discuss clinical obstacles to health care equity, including access to health care and the use of inaccurate language when labelling population groups. We explore the goals and data needed for research under the biopsychosocial model. We describe results from a rheumatic disease literature search that highlights the paucity of studies investigating the molecular influences of systemic exposures. We conclude with a list of considerations and recommendations to help achieve equitable precision medicine.

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Author contributions

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Introduction

The goal of precision medicine is to provide a more precise approach to the prevention, diagnosis and treatment of disease¹. To achieve this goal, precision medicine must be equitable; that is, it must be fairly applicable, available and accessible to all². Unbiased and accessible precision medicine can contribute to reducing avoidable and systemic inequalities in health status, that is, it can contribute to health equity, the state in which everyone has a fair and just opportunity to attain their highest level of health³.

Disparities in prevalence, incidence, clinical and serological manifestations, and outcomes of rheumatic conditions and rheumatological manifestations are well established, with some examples highlighted in Box 1. These disparities are pronounced in under-represented populations, namely racial minority and ethnic groups, medically underserved urban and rural communities, the uninsured and underinsured, older adults, and those with lower education and income⁴. Despite the disproportionate impact of many rheumatic diseases on these communities, the causes of these disparities remain elusive. Identifying the factors that promote disparities is a critical step towards equitable care and precision medicine^{5–7}.

Developing successful precision medicine initiatives necessitates addressing health disparities. Although precision medicine is meant to focus on individual variability (such as genes, environment and lifestyle), these initiatives are predominantly informed by population-level research⁸. The consequence is that if health disparities are not properly identified and addressed in research, precision medicine is poised to worsen health disparities for groups already disadvantaged by current practices and interventions^{8–10}. Frameworks for studying health disparities emphasize the need for ecological models that consider biology and environment, including social factors. In theory, this sounds akin to the needs of precision medicine research but in reality there is substantial isolation of biological research from epidemiological studies on environmental determinants of health.

Despite the recognized influence that social and physical environmental experiences have on rheumatic disease, it is not known how these experiences and exposures interact with biology to influence disease outcomes. To date, rheumatic disease research has largely focused on biological mechanisms without inclusion of effects by environmental exposures. Furthermore, genetic studies frequently fail to acknowledge the fact that non-genetic factors are substantial contributors to the disparities. In addition, the persistent use of vague and arbitrary categories of population differences continues to hamper rigorous and reproducible research¹¹. These issues have resulted in a knowledge gap regarding the interactions between genetic and environmental factors that contribute to disparities in disease outcomes. We explored the extent of this knowledge gap in rheumatic diseases by conducting a literature review of studies that intersected both molecular biology and social determinants of health (SDOH), including racism and discrimination. We identified a striking shortage of literature spanning both molecular and epidemiological disciplines. Further, we identified a strong bias in the amount of research focusing on molecular biology in comparison with epidemiological SDOH. This finding highlights the ‘siloeing’ of research entities and the general challenges (such as data availability and research infrastructure) in implementing a true precision medicine paradigm that considers the full biological and environmental

experiences of a patient; this phenomenon has been identified in other disease categories and has been presented as a cause of hampered progress in alleviating health disparities^{12,13}.

In this Review, we start by discussing clinical obstacles to health care equity, including access to health care and the use of inaccurate language when labelling population groups. We describe the biopsychosocial model and necessary data towards studying health care disparities, followed by a description of existing barriers in research, focusing on limitations in available data, research silos and the subsequent knowledge gap created in rheumatic disease studies. We then propose solutions and considerations, working towards a better understanding of the biology of rheumatic disease in the context of health disparities. Addressing this knowledge gap is expected to improve precision medicine diagnostics and therapeutics for underserved patients, thus working towards a more equitable paradigm in research and clinical practice.

Disparities in health care access

In addition to disparities in disease susceptibility, prevalence and incidence, another source of health disparities occurs in the health care setting. Health care disparities can manifest in different capacities, leading to delayed or deficient patient care and education and poor patient outcomes. Travel distance to receive specialized care is often a deterrent and a major source of delayed patient care. When examining patients in the Medicaid beneficiary cohort (a government health insurance program that provides health care to some of the most vulnerable populations in the USA), poor access to specialized care for patients with systemic lupus erythematosus (SLE) occurred more often in those enrolled in Medicaid than in those with other health insurance¹⁴. Patients only enrolled in Medicaid travelled 11.5 more miles than those with additional or other health insurance and on average more than 19.8 miles to see a rheumatologist¹⁵. Consequently, patients need to use the emergency department not only for acute care but also as their primary source of medication prescriptions¹⁴. In patients with rheumatoid arthritis (RA) in the Canadian universal public health care system, those who lived >100 km from a rheumatologist were 50% less likely to be seen by a rheumatologist within 3 months of a suspected RA diagnosis by a primary care physician and had decreased continuity of care within the first year of diagnosis¹⁶, both of which are important for early initiation of therapy to prevent disability and damage. As a result of these delays, patients have an accumulation of joint damage requiring surgeries¹⁷. Not only is access to specialized clinical care and medications a source of unequal outcomes but it also contributes to a deficiency in patient education, specifically in addressing disease comorbidities, which further promotes health disparities.

These structural barriers to health care access are also deterrents to the achievement of the goals of precision medicine. Access to health care is not guaranteed in many countries. A comparison of health care models in the USA, Austria and Denmark showed that the effects of precision medicine depend on the structure of the local health care system; in contrast to the Austrian and Danish health care systems, the USA for-profit and insurance-based structure increases the risk that precision medicine will exacerbate existing health disparities and structural injustice^{18–20}. In addition to health care coverage, the current high costs of precision medicine therapies also preclude equity by excluding those who cannot access

them. Changes are needed to prevent health care structures and pharmaceutical business models from supporting existing structural injustices and destabilizing egalitarian health policies¹⁸. Such changes include revisiting, monitoring, and regulating drug pricing models, to encompass the values of social equity and solidarity¹⁸.

Describing population groups

Low representation in clinical trials and genomic studies is known to be perpetuated by multiple factors, including geographical distance, mistrust of the health care system, language barriers and fear of encountering implicit bias and stereotyping during care. Under-represented communities are often at a greater risk of poor health outcomes²¹. The confusion about population descriptors and lack of rigorous language when describing population categories continue to stigmatize many communities. Addressing individual biases and using clear and respectful population labels are paramount to realizing the promise of precision medicine²².

Many studies, especially in the USA, describe the epidemiology of rheumatic disease in terms of socially defined, discrete racial categories. Similarly, health disparities research traditionally focuses on self-reported race. However, this methodology poses challenges and limitations. First, race and ethnicity are imperfect proxies for important epidemiological information, including SDOH, such as racism and discrimination, economic stability, health care access and quality, education access, and physical and/or built environmental exposures²³. These social and physical environmental determinants are differentially experienced across racial and ethnic groups owing to historical and contemporary discriminatory policies and practices, resulting in health disparities across groups and geography. Hence, it is not race and ethnicity, but the lifetime of exposures, that contributes to health disparities. Consequently, discrete racial categories are unable to appropriately capture the variability of risks one person might be exposed to in their lifetime. As such, limiting health disparities research to racial categories can impose harm through ascribing risk to arbitrary groupings of heterogeneous individuals while also obscuring the causal exposures facilitating risk²⁴. Another weakness of limiting research to racial categories is that many identities intersect, and thus, risk factors might impose differential or compounded effects. For instance, although increased socioeconomic status (SES) is protective, increased exposure to discrimination has the potential to offset these benefits^{25–27}. In addition, the concept of race is dynamic and changes over time in the wake of administrative decisions and cultural shifts; for example, the list of racial groups on the US Census has changed nearly every decade since the first enumeration in 1790 (ref. 28). Race is also a complex population descriptor because it can be interpreted and measured in many ways (for example, racial identity, racial self-classification, observed race, reflected race)²⁹. Although it may be a useful population descriptor for researchers who wish to measure a consequential form of social status and affiliation, the concept of discrete populations that are static in place and time does not apply to humans.

Another issue is the frequent conflation between race and genetic similarity groups²², often referred to as genetic ancestry groups. Genetic ancestry is a statistical estimate inferred from measures of genetic similarity across individuals using available data, thus without any

relationship to the concept of race. The epidemiological literature reveals rheumatic disease disparities based on ascribed race, and as discussed below, the genetics literature has found rheumatic disease disparities based on genetically inferred groups. However, equating these population descriptors is a fallacy, as race is an imperfect proxy for SDOH, and the other captures genetic risk factors. Altogether, this issue highlights the necessity of a multi-faceted approach to studying health disparities, one that includes both genetic and non-genetic, individual-level and population-level stressors and exposures³⁰. Moving forward, it is critical for researchers to utilize accurate and appropriate population descriptions, such as those described by the National Academies of Science, Engineering, and Medicine²⁸ and by Feero et al.³¹

The biopsychosocial model

The biopsychosocial model was proposed in response to the reductionist paradigm of viewing diseases through a strict 'biomedicine' lens. Instead of viewing the full scope of phenotype and symptoms as explainable by molecular processes (biomedicine model), the biopsychosocial model asserts that health and disease result from an interplay between biological, psychological and social factors³² (Fig. 1a). The biopsychosocial model emphasizes the importance of integrating different domains (such as biological, behavioural, physical and/or built, sociocultural, health care system) and levels (for example, individual, family, community, society). In the context of health disparities, this conceptual framework posits that individuals who perceive certain circumstances as stressful experience a physiological stress response that can be modulated by adverse or protective sociodemographic factors (such as SES), psychological characteristics (for example, depression), behavioural factors (smoking, alcohol use), and coping responses (for example, ability to mobilize social support) to such experiences^{30,33}. Expansions of this model also include physical environmental exposures (for example, air and water quality)³⁴. Such environmental exposures can enact effects independent of individual perception and/or awareness and can be disproportionately distributed among neighbourhoods and by geographic region^{35,36}.

Successful implementation of the biopsychosocial model requires availability of appropriate data, measurements, and instruments for the multiple domains contributing towards health disparities (Fig. 1b). Physical environmental exposures are increasingly available at varying geographic granularity. For example, studies of air quality, ranging from local or regional measures³⁷ to national measures³⁸, highlight the increased prevalence of detrimental environmental exposures among minority and low-income populations. Broadly, environmental factors or determinants to health are usually classified into biological, chemical, physical and social environments. As defined by the WHO, other SDOH include economic security and equality, health behaviours and health care resources^{39,40}. There are many indicators for capturing environmental determinants of health; methodologically, these can be measured via self-reporting (for example, surveys) and/or aggregated data from population statistics with varying granularity^{41,42}. Given the broad domains of environmental determinants of health, it is critical to recognize that any single indicator will be unable to capture the full complexity of an individual's environmental determinants of health, including SDOH⁴⁰. For instance, subjective social status instruments in which

participants rank their circumstances (such as, income) relative to others in their community (for example, social ladders), have been found to capture perceived well-being⁴³, and thus might capture aspects such as perceived discrimination and social stress, whereas multiple deprivation measures might be better suited to capturing material and/or resource-based socioeconomic factors. Given the intersectionality of identities, and thus experiences and exposures, SDOH measures that are multi-faceted (including more than one indicator) and multi-level (that is, individual, community) are more likely to appropriately capture the complexity of these effects^{40,44,45}. In rheumatic diseases, data from each of these broad categories (biological, SDOH) are abundantly available. However, these fields are rarely intertwined to investigate disease outcomes under an ecological, combined molecular and SDOH model, severely hindering progress in health disparities research.

Epidemiological research silo

Decades of epidemiological research of health disparities in rheumatic diseases have highlighted the existence of systemic issues that drive poor outcomes for patients from under-represented and underserved communities (Table 1). For example, multiple social stressors, such as low household income, poverty, unemployment and racial discrimination, are associated with increased risk and severity of SLE^{46,47} and RA^{48,49}. A marked socioeconomic gradient was reported for these diseases, with individuals in the most deprived group being up to 70% more likely to develop the disease than the least deprived group⁴⁹. Low income was associated with greater odds of osteoarthritis⁵⁰ and gout⁵¹, and worse outcomes for systemic sclerosis (SSc)⁵² and sarcoidosis^{53,54}. Social deprivation and social vulnerability were associated with osteoarthritis, RA, ankylosing spondylitis, sarcoidosis, and SSc^{50,55,56}. In countries with lower GDP, patients with psoriatic arthritis had higher levels of disease activity and more patient-reported impact of disease⁵⁷. Also, women, in particular women of understudied and under-represented populations, are disproportionately affected by rheumatic disease; and women, especially African American women, disproportionately experience psychosocial stressors⁵⁵.

Despite stressors co-existing in areas of concentrated poverty and with other environmental factors, protective factors might buffer the negative impacts of stressors⁵⁸. For example, social support decreased depression and anxiety in African American women with SLE^{59–62}, perceived social support improved depression, anxiety and quality of life in patients with RA^{63–65}, and social support and spiritual well-being were associated with life satisfaction in patients with SSc⁶⁶. Additionally, alleviation of stressors can influence disease. For instance, for patients with SLE, exiting poverty can mitigate the strong effect of living in concentrated poverty on disease damage⁶⁷. Most epidemiological research has focused on the identification of risk factors, but understanding the mechanisms and extent to which protective factors can offset risk factors is essential to address health inequities (Table 1).

Although critical, the historical focus on epidemiological issues in rheumatic disparities research has sustained an epidemiological research silo (Fig. 2 and Supplementary Table 1, Supplementary Fig. 1) through its failure to intertwine molecular and biological effects. That is, the molecular and physiological mechanisms through which social and physical and/or built environment exposures affect disparities are unknown. For example, air quality

and particulate exposures have been associated with disease activity and drug response in rheumatic diseases^{68–70}, but the biological mechanisms require more exploration. Similarly, epigenetic marks affect gene expression and can govern cell function and physiological response to environmental factors, including SDOH such as SES^{71,72} and general perceived stress⁷³. Yet, despite the growing awareness of the effect of social stressors on the epigenome, research aimed at identifying and quantifying the regulatory mechanisms through which social exposures influence rheumatic outcomes is only just emerging⁷⁴. Understanding the interplay and underlying mechanisms by which various positive and negative determinants of health influence epigenomic variation, and how the resulting biological changes might contribute to rheumatic health disparities, will enable biomedical research to directly address outcome disparities.

Biological research silo

Large-scale studies into the biological aetiology of rheumatic diseases most commonly focus on genetic variation associated with disease. This line of research has been productive and important. Genome-wide association studies (GWAS) have identified hundreds of genomic loci associated with rheumatic diseases, providing important insights into the biological pathways contributing towards disease. Given the potential to facilitate disease diagnosis, support risk prediction, improve cost and efficiency of trials, and accelerate personalized care, results from these GWAS have been used to construct genetic risk scores (GRS)^{75,76}. Given that many of these risk factors have been reported to vary among populations (for example, along geographic gradients), genetic variation has been proposed as a partial contributor towards disparities^{77,78}. In fact, the 2006–2009 strategic plan of the US National Institute of Arthritis and Musculoskeletal and Skin Diseases prioritized the identification of genetic contributions to health disparities, citing as a rationale that rheumatological conditions, including SSc, SLE and osteoarthritis, cluster in populations targeted by health disparities initiatives⁷⁹. However, to date, few genetic risk factors for rheumatic diseases have been linked to health disparities, which is due, in part, to limitations of genetic data, current data availability and the general siloing of genetic research from pertinent environmental and exposure data.

First, it is crucial to understand the general limitations of genetic data, especially in the context of health disparities research. In genetic studies, individuals are categorized into groups on the basis of genetic similarity to genomic reference groups, such as the 1000 Genomes Project populations⁸⁰. Importantly, however, these genetically assigned categories, often labelled continental ‘ancestry’ groups, are not equivalent to self-identified and socially defined categories of race and ethnicity^{81,82}. Thus, risk allele differences among these genetically defined groups cannot be equated to explaining observed racial health disparities. Furthermore, mapping differences in genetic risk variants among populations requires careful interpretation. Genetic studies disproportionately comprise European-ancestry populations. Even studies including under-represented populations are often more limited in total sample size. Hence, comparison and portability of identified risk variants should always be considered in the context of potential differences in statistical power^{83,84}. Another complicating factor is linkage disequilibrium, which refers to the tendency of linked alleles to be co-inherited. Most GWAS-reported associations

are not causal variants, but instead, ‘tagging’ variants that are highly correlated with the functional variant. Linkage disequilibrium varies by geographically or ancestrally distinct populations. Thus, a genetic association (tagging the causal variant) in one population might not reproduce in another. In studies comprising samples from multiple distinct study populations, linkage disequilibrium can be a powerful fine-mapping tool, as illustrated by SLE studies^{85–87}. Unfortunately, the availability of large, multi-population cohorts remains limited for most rheumatic diseases. The consequence is that, to date, GRS are built upon associated, tagging variants, which frequently show poor predictability in diverse populations⁸⁸. Thus, as they are currently built, these genetic prediction tools do not equally benefit all patients (particularly patients from populations not used to build these tools), precluding health equity in precision medicine⁸⁸. A potential solution is to move towards GRS that are built upon causal versus tagging variants, which requires extensive functional studies to disentangle linkage disequilibrium in associated regions. As reviewed elsewhere⁸⁹, ongoing research aimed at unveiling the aetiology of rheumatic diseases includes individual molecular profiling, incorporating genetic risk, cell-specific transcriptional signatures, epigenomics, mass spectrometry, tissue and in vitro molecular signatures, and environmental factors. However, the majority of current molecular omics research still focuses on individuals with two copies of chromosome X and of genetic European ancestry⁸⁹, and so the results from this progress are not necessarily translatable or applicable to diverse groups.

The second challenge of applying genetics data to health disparities research is that it must be studied within the context of complex disease aetiology, and not in isolation from influencing environmental and gene–environment factors. Importantly, inherited genetic variants, which are fixed within the genome, do not directly capture alterations imposed by environmental and gene–environment factors. Inclusion of additional omics such as transcriptomics (RNA level), proteomics (protein level) and/or epigenomics (for example, cytosine methylation) offers the potential to capture biological changes caused by stress attributable to systemic racism, diet or other lifestyle factors or exposures that more often affect underprivileged patients. Hence, applying genetics and/or omics knowledge also requires comprehensive and high-quality environmental data to control for environmental confounding, to identify gene–environment associations, and to identify the molecular mechanisms through which environmental exposures affect disease outcomes^{90,91}. Genes and environmental exposures are inherited together; individuals with more genetic similarity, such as families or groups from the same region, are also exposed to more environmental similarity^{90,91}. Yet, despite this shared environment, molecular research often negates these factors from studies, contributing to the siloing of biological research. For example, a review of sarcoidosis prevalence emphasized that most family studies focus solely on genetics, without leveraging the opportunity to explore shared environment effects⁹².

Epigenetic studies are well poised to elucidate the relationships between genetics, biology and environmental exposures. Epigenome-wide association studies (EWAS) have identified cell-type-specific DNA methylation changes associated with multiple rheumatic diseases⁷⁸. As reviewed, although DNA methylation varies among population groups, and this variation is partially explained by their distinct genetic ancestry, environmental factors not captured by genetic ancestry are important contributors to variation in DNA methylation. This fact

supports the notion that an interaction between environmental, genetic and epigenetic factors underlies health disparities in rheumatic conditions. Mounting evidence suggests that environmental exposures influence epigenetic modifications and trigger alterations in multiple regulatory mechanisms that interact to create a systemic response^{93,94}. For example, air pollution exposure downregulates hsa-miR-137, which leads to a pro-inflammatory state that contributes to the pathogenesis of RA⁹⁵. In rheumatic diseases, EWAS have largely focused on epigenetic associations with disease, without incorporation of environmental factors linked to determinants of health.

Our review of the literature shows a considerable bias in the number of studies on biological outcomes compared with epidemiological, SDOH research (Supplementary Table 1). On average, the amount of published biological research was 106:1 compared with SDOH research across ten rheumatic diseases (range: 35–271 times). As explored below (in The knowledge gap from research silos), overlap between biological and SDOH research is minimal (<1% for each of the rheumatic diseases explored) (Fig. 2). Despite the accepted influence of environmental factors on cell processes, including the role of stress in inflammation^{96,97} and diseases such as SLE, RA and Sjögren's syndrome⁹⁸, exploration of the biological mechanisms that these exposures enact within the context of health disparities research is limited.

The knowledge gap from research silos

In our review of ten major rheumatic diseases, we identified 71 unique manuscripts that spanned both molecular biology and SDOH topics in the manuscript (Supplementary Table 2). The majority (60.5%) of the 71 manuscripts were classified as reviews, perspectives or protocol papers (Supplementary Fig. 2). Of manuscripts classified as original research, most were genetic studies stratified by race or that adjusted for SDOH in their analytic models. Notably, none reported on the mechanistic links between SDOH and molecular biology outcomes. We recognize that some biologically centred studies that included factors such as income or poverty, but not specific terms such as SDOH or SES, might have been excluded from our search. However, we note that including such factors in the absence of common SDOH or SES identifiers fails to acknowledge their context within a biopsychosocial model and their potential relevance to health disparities. Hence, we limited our intersection search to those that explicitly denoted health disparities, racism, SES and/or SDOH in the manuscript. Altogether, the scarcity of articles identified emphasizes the current knowledge gap of biological–SDOH mechanisms within rheumatic diseases.

After reviews and commentaries, the majority of identified rheumatological research that included biological and epidemiological features could be classified as genetic risk studies that adjusted for SDOH, primarily using measures of SES. Of note, Cui et al. studied risk prediction for incident SLE among women in the Nurse's health study cohorts and found that prediction models that included genetics, family history and lifestyle (including income and US geographic region) yielded better performance than models built solely on genetics⁹⁹. This finding highlights the value of incorporating variables beyond biology in prediction models. Other studies focused on assessing genetic risk while adjusting for an SES factor, including single variables (for example, income and education level), social

ladders and indices of multiple deprivation. Although multiple deprivation indices and social ladder surveys are more multi-faceted than single variables, we note that these are not without limitations^{45,100} and cannot be considered to fully capture the complexity of SDOH. That is, the absence of SDOH effects in a biological model should not be concluded when only a limited measure (such as income) was considered. In our search, we identified several examples in which potential influences of SDOH were downplayed because genetic associations remained after adjustment for single-faceted SDOH variables, further illustrating the siloing of SDOH and molecular research.

Breaking research silos

The results of this literature search highlight the need for growth in the field. Here, we outline some key considerations and potential solutions towards enabling biopsychosocial research in rheumatic diseases and offering paths towards identifying and alleviating health disparities (Box 2).

Structural barriers

So far, and across disciplines, addressing equity in precision medicine has focused on increasing inclusivity in research. Two leading precision medicine initiatives, the All of Us research program (USA) and Genomics England (UK), placed diversity and inclusion at the core of their efforts to promote equity. However, as argued by Galasso¹⁰¹, efforts at inclusion upstream (by removing barriers to participation in research) do not correspond with efforts for inclusion downstream (by facilitating access to the benefits deriving from precision medicine), and this imbalance jeopardizes the equitable goals of the programmes. For example, to address the objective upstream barriers (such as time, technological literacy, language fluency) and subjective upstream barriers to participation (including mistrust, fear and stigma), All of Us implemented a comprehensive series of strategies to facilitate inclusive participation by addressing communities' mistrust, mobility, language and tech-literacy barriers¹⁰², such as including educational content in several languages, assistance via telephone, arranging home visits and providing dedicated informative material prepared in collaboration with community members. Legal barriers, such as inadequate privacy and anti-discrimination protections for research participants, and practices by research sponsors that tolerate and entrench disparities, also limit diversity and inclusion in genomic research¹⁰³.

Despite efforts on inclusion upstream, downstream inclusion has remained challenging. Structural barriers preventing the affordability and availability of precision medicine outputs are the chief downstream obstacle, most notably poverty. Access to biomedical benefits are constrained by the costs of private structures and by the long waiting lists and under-resourcing of publicly funded health care¹⁰¹. For example, the costs of CAR-T therapies make them unavailable to individuals or countries who cannot afford them. Legal barriers can also limit the implementation of equitable precision medicine, including lack of health coverage and funding for follow-up care, and failure to use law to ensure access to genomic medicine¹⁰³. Structural factors can also prevent behavioural or lifestyle changes. Because the rheumatology community is acutely aware that health disparities and lifestyle choices

negatively impact disease outcomes, our discipline is uniquely positioned to advocate for positive, broad change. However, owing to the mistrust that exists towards the health care and research communities, academic professionals need to form relationships with trusted community members who understand the needs of patients and can influence their lifestyle choices, thereby creating lasting change. Consequently, the formation of community–academic partnerships is a solution that helps engage the community in medical care, education and research, while highlighting the social resources needed for a holistic approach to patient care¹⁰⁴. These partnerships are also positioned to examine the effect of specific SDOH in rheumatic diseases within a community¹⁰⁵.

Another issue is the current focus on individualized risk scores and preventive strategies at the cost of structural drivers of health, including racism, and prevention of disease. This focus on the individual might increase responsabilization and stigmatization of individuals, while neglecting how health outcomes are inseparable from environmental and structural factors beyond the individual's control¹⁸. This issue is particularly relevant in societies in which historical and contemporary discrimination not only cause health disparities but continuously prohibit opportunities for lifestyle changes for those at highest risk owing to a lack of basic resources and environmental opportunities for making healthier choices¹⁸. Recommendations can guide researchers on how to address the impacts of structural drivers of health, including racism, at all stages of the research process⁵. Precision medicine can catalyse knowledge and attention to inform and incentivize sociopolitical reforms to reduce social inequalities and inequities¹⁰¹. Specifically, All of Us and Genomics England can generate important information on social and environmental determinants of health, which might not be actionable for research participants, but would be actionable for institutions and policy makers¹⁰¹. This is the goal of precision public health.

Multidisciplinary teams

Diversity in backgrounds and expertise is crucial to break the current research silos and address health disparities in precision medicine. Transdisciplinary collaboration is also needed between biological and epidemiological scientists, academics and clinicians, and partnerships with institutions, community groups and patients that represent diverse perspectives. Diverse and transdisciplinary teams are needed at all stages, from study design (what biological and SDOH measures to collect, what communities to include), to action (how to analyse and interpret results), writing and dissemination of results (how to communicate results to benefit instead of discriminate against vulnerable groups), and implementation of strategies to mitigate health disparities. A study focused on precision medicine research teams found the following points: one, existing hierarchies and power structures in the research ecosystem compound challenges for equitable diversification of teams; two, tokenism and instrumental diversity (to advance corporate interests) jeopardize goals to diversify research teams and risk merely transient and superficial diversification; and three, the siloing of the expertise of under-represented team members to frontline and diversity-only activities might perpetuate a turnstile effect, in which these team members move from study to study laterally, or altogether leave the field because of the lack of advancement opportunities¹⁰⁶. Without considering the power structure within research teams, tokenism can be misrecognized as inclusion¹⁰⁶.

Furthermore, to address health disparities in precision medicine, commitment from biotechnology and pharma industries, health care systems, and governments is also needed²¹. The inclusion of legal experts is needed to address legal barriers that limit broad inclusion in genomic research and the development of precision medicine to advance health equity¹⁰³. Policymakers are essential to assess and address the effects of the sociopolitical, economic and structural contexts of health care implementation¹⁸. Without concerted public health action, health disparities could widen in the next decade⁴.

Diversity in data resources

Identifying and addressing health disparities in rheumatic diseases requires greater sample diversity in datasets¹⁰⁷. There has been a growing push to make GWAS analyses more equitable through sample diversity and using genotyping platforms better suited to capturing global variation. One such example is the MEGAchip, which is a consortium effort that developed a genotyping array to better capture genetic diversity across global populations^{84,108}. For sequencing studies, reference genomes have been developed that are more appropriate for capturing rare sequencing variants in diverse populations^{109,110}. Importantly, diversity in biological data is also needed beyond studies strictly identifying genetic risk variants. As described above, it is essential to pinpoint the functional variants contributing to disease, requiring extensive functional annotations and tissue-specific data. Repositories used for these goals have not been representative of global diversity. Long et al. explored this issue among datasets used to link genetic variants to gene expression (expression quantitative trait loci) and found that three major resources overwhelmingly comprised European ancestry samples (82–95% of samples)¹¹¹. The lack of diversity in large datasets is even more apparent for cohorts containing environmental and lifestyle data, particularly for rheumatic diseases. For example, the US National Institutes of Health-funded Polygenic Risk Methods in Diverse Populations Consortium pools genomic and phenotypic information from diverse populations¹¹². However, at present, the phenotypic and environmental data are limited.

The paucity of large and diverse population-based cohorts with validated diagnoses has been a substantial barrier to better understanding the true clinical burden of disease, as well as the many unanswered questions related to treatment, health care access, and natural history¹¹³. The Environmental Influences in Child Health Outcomes, All Of Us¹¹⁴, and Genomics England programmes were created to mitigate against these disparities¹¹⁵. However, given that these programmes reflect broad (non-disease-focused) recruitment efforts, sufficient numbers for conducting studies in rheumatic diseases remains challenging. Efforts to include communities with worse and better outcomes will be important, to fully understand the interplay among risk factors. Researchers collecting biological samples should make efforts to collect granular sociocultural and environmental data, moving beyond the scope of the limited racial and ethnic categories currently used by the US Office of Management and Budget.

As previously described, many instruments can be used to capture various aspects of SDOH. Although we advocate for using multi-dimensional tools that capture both materials and/or resources (for example, income) and exposures (such as stress, environment), the

feasibility might vary by study. For any instrument used, it is critical to be cognizant of and report limitations of the study (for example, factors not captured by the data). Electronic health record (EHR) data might provide a promising venue to facilitate SDOH data collection; however, logistical challenges, such as infrastructure and consensus of standards, might affect the speed of implementation¹¹⁶. The EU-funded SPIDeRR consortium (Stratification of Patients using advanced Integrative modelling of Data Routinely acquired for diagnosing Rheumatic complaints) is aimed at leveraging EHR data from seven countries to streamline early diagnosis of rheumatic diseases. In addition to using GRS for disease differentiation, SPIDeRR is also aimed at investigating the interplay between genetics and the environment⁷⁵.

Infrastructure for research development

Patients with rheumatic diseases require a transformation in both patient care and research infrastructure to address current and future health disparities. As the benefits of collaborations in team science are increasingly recognized, utilizing international collaborations is an additional method to diversify patient recruitment to investigate and minimize disparities in rheumatic disease. For example, in China, a clinical trial focused on multidisciplinary care for patients with SLE showed a substantial decline in disease activity in the intervention group and an improvement of health quality¹¹⁷. A subsequent study reviewed the pros and cons of this approach, specifically in the care of patients with lupus nephritis¹¹⁸. Another example is the Sjögren's International Collaborative Clinical Alliance, which was created to expand the infrastructure for engagement and to be used as a research tool to better understand the pathogenesis of Sjögren's disease. Several publications to date have used this collaboration as the basis for manuscripts, including investigating associations between clinical disease manifestations and autoantibody profiles¹¹⁹. This international collaborative approach broadens not only the number of potential patients but also invites the participation of diverse researchers, which will enlarge the range of research topics and ideas to address research disparities.

Building multidisciplinary teams and more robust data resources will require significant infrastructure. Previous inquiries on the slowed progress and siloing of health equity research identified funding as a meaningful influence on multidisciplinary work^{120,121}. That is, funding mechanisms and priorities have the potential to facilitate the bridging or sub-division of disciplines. Although historic commitments have been made towards health disparities research, including the US Healthy People 2010 programme (funded in 2000) and the aforementioned 2006–2009 strategic plan of the US National Institute of Arthritis and Musculoskeletal and Skin Diseases, we posit that these were inadvertently, largely, siloing infrastructures — the former focusing on epidemiological initiatives and the latter prioritizing the identification of genetic contributions to health disparities. Opportunely, in 2023, the US National Institutes of Health began funding projects to design, develop and implement an Exposome in Autoimmune Diseases Collaborating Teams (EXACT) Network¹²². Its goal is to enable institutions to plan research strategies and develop partnerships, infrastructure and capabilities. The EXACT initiative is envisioned as a multisite, collaborative network that will adopt a team science approach to produce a systems-level understanding of the role of the exposome in autoimmune diseases. Focused

investment is needed for similar projects and programmes that will combine clinical and analytical teams to collect and integrate clinical, omics and exposure data to enable analyses focused on elucidating how specific exposures govern biological responses in patients with rheumatic diseases. Longitudinal follow-up and collection of biospecimens is also challenging¹¹³; to address this limitation, the US Centers for Disease Control and Prevention has funded five population-based SLE registries¹⁰⁷.

Disseminating research responsibly

Finally, understanding and alleviating health disparities requires care in the reporting and dissemination of results. These studies have the potential to inform diagnoses, interventions and future policies, but they also have the potential to produce harm. As previously discussed, researchers should avoid conflating self-reported race with genetic ancestry. However, even with repeated emphasis in reporting guidelines^{11,31,123} distinctions can still be blurred. For instance, owing to sampling strategies and analytical challenges, some studies still assign genetic ancestry categorically rather than as a continuum, which can reinforce the erroneous interpretation that discrete continental population labels reflect discrete genetic differences among samples¹²⁴. Additionally, studies must thoroughly acknowledge limitations of findings, such as explicit definitions of what environmental and/or social factors might not have been captured or included in analyses and results. These issues are also pertinent in the age of large language models, which are increasingly available to and leveraged by the public and search engines. These models synthesize large quantities of data and can be influenced by biases present in training data¹²⁵ with the potential to reiterate racist ideologies¹²⁶. Thus, all roles contributing towards health disparities research, including researchers, journal editors and peer reviewers must remain diligent in assessing manuscripts for clarity and precision on these issues.

Conclusions

Although precision medicine has been promoted for over a decade, a lack of understanding of the effects of determinants of health on health disparities remains a barrier to achieving equitable access to precision medicine²¹. To date, crossover between molecular and SDOH research groups remains limited; this challenge is pervasive across disciplines, but awareness of the problems it poses is growing^{12,13}. We have illustrated the disciplinary siloing between molecular and epidemiological research by quantifying the current publication gap of integrative research across ten rheumatic diseases. Current work has already shown how inclusion of additional exposures and SDOH can improve biological risk models, but more data are needed to further this area of research. Until we diversify rheumatic disease research, it will remain impossible to implement precision medicine that is informed by both environmental and genetic factors for all patient demographics. Our presented solutions include breaking the epidemiological and biological silos, as well as commitments to equity and structural reform. These changes are necessary to elucidate how exposures affect the heterogeneous molecular and cellular pathways leading to pathology, and might highlight novel approaches to avoiding or neutralizing interactions that contribute to rheumatic disease. We note that these challenges are not unique to rheumatic diseases and thus there is benefit in uniting efforts across disease-focused fields (for example, towards

standardized SDOH and environmental exposure data, and society-level changes towards better inclusion). The continued development of EHR data, high-throughput omics and molecular profiling offers great opportunities but only if the field works to ensure these data are truly representative of the complex biological and environmental relationships within patient populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. National Human Genome Research Institute. Precision Medicine. <https://www.genome.gov/genetics-glossary/Precision-Medicine> (2024).
2. Costa A et al. From “Inclusion in What” to “Equity in What”: (Re)thinking the question of in/equity in precision medicine and health. *Am. J. Bioeth.* 24, 89–91 (2024).
3. CDC. Health Equity. <https://www.cdc.gov/healthequity/whatis/index.html> (2024).
4. Khoury MJ et al. Health equity in the implementation of genomics and precision medicine: a public health imperative. *Genet. Med.* 24, 1630–1639 (2022). [PubMed: 35482015]
5. Allen CG et al. Extending an antiracism lens to the implementation of precision public health interventions. *Am. J. Public. Health* 113, 1210–1218 (2023). [PubMed: 37651661]
6. Matthew DB Two threats to precision medicine equity. *Ethn. Dis.* 29, 629–640 (2019). [PubMed: 31889768]
7. Odutola J & Ward MM Ethnic and socioeconomic disparities in health among patients with rheumatic disease. *Curr. Opin. Rheumatol.* 17, 147–152 (2005). [PubMed: 15711226]
8. Khoury MJ, Iademarco MF & Riley WT Precision public health for the era of precision medicine. *Am. J. Prev. Med.* 50, 398–401 (2016). [PubMed: 26547538]
9. Cohn EG, Henderson GE & Appelbaum PS Distributive justice, diversity, and inclusion in precision medicine: what will success look like? *Genet. Med.* 19, 157–159 (2017). [PubMed: 27490116]
10. Sabatello M Precision medicine, health disparities, and ethics: the case for disability inclusion. *Genet. Med.* 20, 397–399 (2018). [PubMed: 28771252]
11. Cho MK et al. Words matter: the language of difference in human genetics. *Genet. Med.* 25, 100343 (2023). [PubMed: 36524987]
12. Lopez KN & Fuentes-Afflick E Engaging pediatric subspecialists in pursuit of health equity-breaking out of the silo. *JAMA Pediatr.* 176, 841–842 (2022). [PubMed: 35849417]
13. Richardson A, Darst B, Wojcik G, Wagle N & Haricharan S Research silos in cancer disparities: obstacles to improving clinical outcomes for underserved patient populations. *Clin. Cancer Res.* 29, 1194–1199 (2023). [PubMed: 36638200]
14. Pryor KP, Barbhuiya M, Costenbader KH & Feldman CH Disparities in lupus and lupus nephritis care and outcomes among US Medicaid beneficiaries. *Rheum. Dis. Clin. North. Am.* 47, 41–53 (2021). [PubMed: 34042053]
15. Gillis JZ et al. Medicaid and access to care among persons with systemic lupus erythematosus. *Arthritis Rheum.* 57, 601–607 (2007). [PubMed: 17471527]
16. Widdifield J et al. Access to rheumatologists among patients with newly diagnosed rheumatoid arthritis in a Canadian universal public healthcare system. *BMJ Open.* 4, e003888 (2014).

17. Barnabe C Disparities in rheumatoid arthritis care and health service solutions to Equity. *Rheum. Dis. Clin. North. Am.* 46, 685–692 (2020). [PubMed: 32981645]
18. Green S, Prainsack B & Sabatello M The roots of (in)equity in precision medicine: gaps in the discourse. *Per. Med.* 21, 5–9 (2024). [PubMed: 38088178]
19. Green S, Prainsack B & Sabatello M Precision medicine and the problem of structural injustice. *Med. Health Care Philos.* 26, 433–450 (2023). [PubMed: 37231234]
20. Tabery J *Tyranny of the Gene. Personalized Medicine and its Tread to Public Health.* (Penguin Random House, 2023).
21. Ory MG, Adepoju OE, Ramos KS, Silva PS & Vollmer Dahlke D Health equity innovation in precision medicine: current challenges and future directions. *Front. Public. Health* 11, 1119736 (2023). [PubMed: 36875406]
22. Ramos PS & Lim SS Clarity for the language of race, ethnicity and genetic ancestry in rheumatology. *Nat. Rev. Rheumatol* 384, 474–454 (2024).
23. Borrell LN et al. Race and genetic ancestry in medicine — a time for reckoning with racism. *N. Engl. J. Med.* 384, 474–480 (2021). [PubMed: 33406325]
24. Gordon NP, Lin TY, Rau J & Lo JC Aggregation of Asian-American subgroups masks meaningful differences in health and health risks among Asian ethnicities: an electronic health record based cohort study. *BMC Public. Health* 19, 1551 (2019). [PubMed: 31760942]
25. Hudson DL et al. Are benefits conferred with greater socioeconomic position undermined by racial discrimination among African American men? *J. Mens Health* 9, 127–136 (2012). [PubMed: 22707995]
26. Colen CG, Ramey DM, Cooksey EC & Williams DR Racial disparities in health among nonpoor African Americans and Hispanics: the role of acute and chronic discrimination. *Soc. Sci. Med.* 199, 167–180 (2018). [PubMed: 28571900]
27. Williams DR, Mohammed SA, Leavell J & Collins C Race, socioeconomic status, and health: complexities, ongoing challenges, and research opportunities. *Ann. NY Acad. Sci.* 1186, 69–101 (2010). [PubMed: 20201869]
28. National Academies of Sciences, Engineering & Medicine. *Using Population Descriptors in Genetics and Genomics Research: A New Framework for an Evolving Field.* (The National Academies Press, 2023).
29. Roth WD The multiple dimensions of race. *Ethn. Racial Stud.* 39, 1310–1338 (2016).
30. Chae DH, Nuru-Jeter AM, Lincoln KD & Francis DD Conceptualizing racial disparities in health: advancement of a socio-psychobiological approach. *Du Bois Rev.* 8, 63–77 (2011).
31. Feero WG et al. Guidance on use of race, ethnicity, and geographic origin as proxies for genetic ancestry groups in biomedical publications. *JAMA* 331, 1276–1278 (2024). [PubMed: 38470200]
32. Engel GL The need for a new medical model: a challenge for biomedicine. *Science* 196, 129–136 (1977). [PubMed: 847460]
33. Clark R, Anderson NB, Clark VR & Williams DR Racism as a stressor for African Americans. A biopsychosocial model. *Am. Psychol* 54, 805–816 (1999). [PubMed: 10540593]
34. Gee GC & Payne-Sturges DC Environmental health disparities: a framework integrating psychosocial and environmental concepts. *Env. Health Perspect.* 112, 1645–1653 (2004). [PubMed: 15579407]
35. Harrell CJ et al. Multiple pathways linking racism to health outcomes. *Du Bois Rev.* 8, 143–157 (2011). [PubMed: 22518195]
36. Martenies SE, Milando CW, Williams GO & Batterman SA Disease and health inequalities attributable to air pollutant exposure in Detroit, Michigan. *Int. J. Environ. Res. Public Health* 14, 1243 (2017). [PubMed: 29048385]
37. Chambliss SE et al. Local- and regional-scale racial and ethnic disparities in air pollution determined by long-term mobile monitoring. *Proc. Natl Acad. Sci. USA* 118, e2109249118 (2021). [PubMed: 34493674]
38. Jbaily A et al. Air pollution exposure disparities across US population and income groups. *Nature* 601, 228–233 (2022). [PubMed: 35022594]

39. Braveman P Health disparities and health equity: concepts and measurement. *Annu. Rev. Public. Health* 27, 167–194 (2006). [PubMed: 16533114]
40. World Health Organization. Social determinants of health. <https://www.who.int/health-topics/social-determinants-of-health> (2024).
41. Schuurman N, Bell N, Dunn JR & Oliver L Deprivation indices, population health and geography: an evaluation of the spatial effectiveness of indices at multiple scales. *J. Urban. Health.: Bull. NY Acad. Med* 84, 591–603 (2007).
42. Penman-Aguilar A et al. Measurement of health disparities, health inequities, and social determinants of health to support the advancement of health equity. *J. Public Health Manag. Pract.* 22, S33–S42 (2016). [PubMed: 26599027]
43. Andersson MA An odd ladder to climb: socioeconomic differences across levels of subjective social status. *Soc. Indic. Res.* 136, 621–643 (2018).
44. Kolak M, Bhatt J, Park YH, Padron NA & Molefe A Quantification of neighborhood-level social determinants of health in the continental United States. *JAMA Netw. Open.* 3, e1919928 (2020). [PubMed: 31995211]
45. Deas I, Robson B, Wong C & Bradford M Measuring neighbourhood deprivation: a critique of the index of multiple deprivation. *Environ. Plan. C: Gov. Policy* 21, 883–903 (2003).
46. Ramos PS Integrating genetic and social factors to understand health disparities in lupus. *Curr. Opin. Rheumatol.* 33, 598–604 (2021). [PubMed: 34468428]
47. Buie J et al. Disparities in lupus and the role of social determinants of health: current state of knowledge and directions for future research. *ACR Open. Rheumatol.* 5, 454–464 (2023). [PubMed: 37531095]
48. Romao VC & Fonseca JE Etiology and risk factors for rheumatoid arthritis: a state-of-the-art review. *Front. Med* 8, 689698 (2021).
49. Conrad N 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* 401, 1878–1890 (2023). [PubMed: 37156255]
50. Callahan LF, Cleveland RJ, Allen KD & Golightly Y Racial/ethnic, socioeconomic, and geographic disparities in the epidemiology of knee and hip osteoarthritis. *Rheum. Dis. Clin. North. Am.* 47, 1–20 (2021). [PubMed: 34042049]
51. McCormick N et al. Racial and sex disparities in gout prevalence among US adults. *JAMA Netw. Open.* 5, e2226804 (2022). [PubMed: 35969396]
52. Moore DF & Steen VD Racial disparities in systemic sclerosis. *Rheum. Dis. Clin. North. Am.* 46, 705–712 (2020). [PubMed: 32981647]
53. Sharp M, Eakin MN & Drent M Socioeconomic determinants and disparities in sarcoidosis. *Curr. Opin. Pulm. Med.* 26, 568–573 (2020). [PubMed: 32732595]
54. Harper LJ et al. Income and other contributors to poor outcomes in U.S. patients with sarcoidosis. *Am. J. Respir. Crit. Care Med.* 201, 955–964 (2020). [PubMed: 31825646]
55. Chae DH et al. Racial discrimination, disease activity, and organ damage: the Black Women's Experiences Living with Lupus (BeWELL) study. *Am. J. Epidemiol.* 188, 1434–1443 (2019). [PubMed: 31062841]
56. Li X, Sundquist J, Hamano T & Sundquist K Neighborhood deprivation and risks of autoimmune disorders: a national cohort study in Sweden. *Int. J. Environ. Res. Public Health* 16, 3798 (2019). [PubMed: 31601008]
57. Lucasson F et al. Disparities in healthcare in psoriatic arthritis: an analysis of 439 patients from 13 countries. *RMD Open* 8, e002031 (2022). [PubMed: 35523519]
58. Zimmerman MA et al. Adolescent resilience: promotive factors that inform prevention. *Child. Dev. Perspect.* 7, 215–220 (2013).
59. Williams EM et al. Cytokine balance and behavioral intervention; findings from the Peer Approaches to Lupus Self-Management (PALS) project. *Hum. Immunol.* 78, 574–581 (2017). [PubMed: 28716698]
60. Williams EM et al. Peer-to-peer mentoring for African American women with lupus: a feasibility pilot. *Arthritis Care Res.* 70, 908–917 (2018).

61. Flournoy-Floyd M et al. We Would Still Find Things to Talk About”: assessment of mentor perspectives in a systemic lupus erythematosus intervention to improve disease self-management, empowering SLE patients. *J. Natl Med. Assoc* 110, 182–189 (2018). [PubMed: 29580453]
62. Jordan J, Thompson NJ, Dunlop-Thomas C, Lim SS & Drenkard C Relationships among organ damage, social support, and depression in African American women with systemic lupus erythematosus. *Lupus* 28, 253–260 (2019). [PubMed: 30482093]
63. Pitsilka DA, Kafetsios K & Niakas D Social support and quality of life in patients with rheumatoid arthritis in Greece. *Clin. Exp. Rheumatol.* 33, 27–33 (2015). [PubMed: 25437270]
64. Nebhinani N, Mattoo SK & Wanchu A Quality of life, social support, coping strategies, and psychiatric morbidity in patients with rheumatoid arthritis. *J. Neurosci. Rural. Pract.* 13, 119–122 (2022). [PubMed: 35110931]
65. Zyrianova Y et al. Depression and anxiety in rheumatoid arthritis: the role of perceived social support. *Ir. J. Med. Sci.* 175, 32–36 (2006).
66. Chen YT et al. Factors associated with life satisfaction in systemic sclerosis: examining the moderating roles of social support and spiritual well-being. *J. Scleroderma Relat. Disord.* 8, 107–112 (2023). [PubMed: 37283281]
67. DeQuattro K & Yelin E Socioeconomic status, health care, and outcomes in systemic lupus erythematosus. *Rheum. Dis. Clin. North. Am.* 46, 639–649 (2020). [PubMed: 32981641]
68. Adami G et al. Environmental air pollution is a predictor of poor response to biological drugs in chronic inflammatory arthritides. *ACR Open. Rheumatol.* 3, 451–456 (2021). [PubMed: 34060251]
69. Adami G et al. Association between environmental air pollution and rheumatoid arthritis flares. *Rheumatology* 60, 4591–4597 (2021). [PubMed: 33470401]
70. Wu Q et al. Association between traffic-related air pollution and hospital readmissions for rheumatoid arthritis in Hefei, China: a time-series study. *Env. Pollut.* 268, 115628 (2021). [PubMed: 33049484]
71. Lam LL et al. Factors underlying variable DNA methylation in a human community cohort. *Proc. Natl Acad. Sci. USA* 109, 17253–17260 (2012). [PubMed: 23045638]
72. Borghol N et al. Associations with early-life socio-economic position in adult DNA methylation. *Int. J. Epidemiol.* 41, 62–74 (2012). [PubMed: 22422449]
73. Vidal AC et al. Maternal stress, preterm birth, and DNA methylation at imprint regulatory sequences in humans. *Genet. Epigenet* 6, 37–44 (2014). [PubMed: 25512713]
74. Vara EL et al. Social Factors, Epigenomics and Lupus in African American Women (SELA) Study: protocol for an observational mechanistic study examining the interplay of multiple individual and social factors on lupus outcomes in a health disparity population. *Lupus Sci. Med* 9, e000698 (2022). [PubMed: 35768168]
75. Vaskimo LM et al. The application of genetic risk scores in rheumatic diseases: a perspective. *Genes* 14, 2167 (2023). [PubMed: 38136989]
76. Polygenic Risk Score Task Force of the International Common Disease Alliance. Responsible use of polygenic risk scores in the clinic: potential benefits, risks and gaps. *Nat. Med.* 27, 1876–1884 (2021). [PubMed: 34782789]
77. Ramos PS Population genetics and natural selection in rheumatic disease. *Rheum. Dis. Clin. North. Am.* 43, 313–326 (2017). [PubMed: 28711136]
78. Lanata CM, Blazer A & Criswell LA The contribution of genetics and epigenetics to our understanding of health disparities in rheumatic diseases. *Rheum. Dis. Clin. North. Am.* 47, 65–81 (2021). [PubMed: 34042055]
79. Sankar P et al. Genetic research and health disparities. *JAMA* 291, 2985–2989 (2004). [PubMed: 15213210]
80. 1000 Genomes Project Consortium et al. A global reference for human genetic variation. *Nature* 526, 68–74 (2015). [PubMed: 26432245]
81. Johnson R et al. Leveraging genomic diversity for discovery in an electronic health record linked biobank: the UCLA ATLAS community health initiative. *Genome Med.* 14, 104 (2022). [PubMed: 36085083]

82. Yudell M, Roberts D, DeSalle R & Tishkoff S SCIENCE AND SOCIETY. Taking race out of human genetics. *Science* 351, 564–565 (2016). [PubMed: 26912690]
83. Martin AR et al. Human demographic history impacts genetic risk prediction across diverse populations. *Am. J. Hum. Genet.* 100, 635–649 (2017). [PubMed: 28366442]
84. Wojcik GL et al. Genetic analyses of diverse populations improves discovery for complex traits. *Nature* 570, 514–518 (2019). [PubMed: 31217584]
85. Alarcon-Riquelme ME et al. Genome-wide association study in an Amerindian Ancestry population reveals novel systemic lupus erythematosus risk loci and the role of European admixture. *Arthritis Rheumatol.* 68, 932–943 (2016). [PubMed: 26606652]
86. Langefeld CD et al. Transancestral mapping and genetic load in systemic lupus erythematosus. *Nat. Commun.* 8, 16021 (2017). [PubMed: 28714469]
87. Patel ZH et al. A plausibly causal functional lupus-associated risk variant in the STAT1–STAT4 locus. *Hum. Mol. Genet.* 27, 2392–2404 (2018). [PubMed: 29912393]
88. Martin AR et al. Clinical use of current polygenic risk scores may exacerbate health disparities. *Nat. Genet.* 51, 584–591 (2019). [PubMed: 30926966]
89. Guthridge JM, Wagner CA & James JA The promise of precision medicine in rheumatology. *Nat. Med.* 28, 1363–1371 (2022). [PubMed: 35788174]
90. Feldman MW & Lewontin RC The heritability hang-up. *Science* 190, 1163–1168 (1975). [PubMed: 1198102]
91. Moore DS & Shenk D The heritability fallacy. *Wiley Interdiscip. Rev. Cogn. Sci.* 8, e1400 (2017).
92. Ramos-Casals M et al. How the frequency and phenotype of sarcoidosis is driven by environmental determinants. *Lung* 197, 427–436 (2019). [PubMed: 31190130]
93. Peschken CA Health disparities in systemic lupus erythematosus. *Rheum. Dis. Clin. North. Am.* 46, 673–683 (2020). [PubMed: 32981644]
94. Wu H, Eckhardt CM & Baccarelli AA Molecular mechanisms of environmental exposures and human disease. *Nat. Rev. Genet.* 24, 332–344 (2023). [PubMed: 36717624]
95. Tsai MH et al. Urban particulate matter enhances ROS/IL-6/COX-II production by inhibiting MicroRNA-137 in synovial fibroblast of rheumatoid arthritis. *Cells* 9, 1378 (2020). [PubMed: 32498294]
96. Stojanovich L Stress and autoimmunity. *Autoimmun. Rev.* 9, A271–A276 (2010). [PubMed: 19931651]
97. Katrinli S, Oliveira NCS, Felger JC, Michopoulos V & Smith AK The role of the immune system in posttraumatic stress disorder. *Transl. Psychiatry* 12, 313 (2022). [PubMed: 35927237]
98. Song H et al. Association of stress-related disorders with subsequent autoimmune disease. *JAMA* 319, 2388–2400 (2018). [PubMed: 29922828]
99. Cui J et al. Risk prediction models for incident systemic lupus erythematosus among women in the Nurses' health study cohorts using genetics, family history, and lifestyle and environmental factors. *Semin. Arthritis Rheum.* 58, 152143 (2023). [PubMed: 36481507]
100. Franzini L & Fernandez-Esquer ME The association of subjective social status and health in low-income Mexican-origin individuals in Texas. *Soc. Sci. Med.* 63, 788–804 (2006). [PubMed: 16580107]
101. Galasso I Precision medicine for whom? Public health outputs from “Genomics England” and “All of Us” to make up for upstream and downstream exclusion. *Am. J. Bioeth.* 24, 71–85 (2024).
102. All of Us research program. Operational Protocol. <https://allofus.nih.gov/about/all-us-research-program-protocol> (2024).
103. Wolf SM, Bonham VL & Bruce MA How can law support development of genomics and precision medicine to advance health equity and reduce disparities? *Ethn. Dis* 29, 623–628 (2019). [PubMed: 31889767]
104. Borgia RE & Alarcon GS Community-engaged research to address health disparities in systemic lupus erythematosus. *Arthritis Care Res.* 73, 305–307 (2021).

105. Leatherwood C et al. Community-engaged research: leveraging community-academic partnerships to reduce disparities and inequities in lupus care. *Rheum. Dis. Clin. North. Am.* 47, 109–118 (2021). [PubMed: 34042050]
106. Jeske M et al. Beyond inclusion: enacting team equity in precision medicine research. *PLoS ONE* 17, e0263750 (2022). [PubMed: 35130331]
107. Drenkard C & Lim SS Update on lupus epidemiology: advancing health disparities research through the study of minority populations. *Curr. Opin. Rheumatol.* 31, 689–696 (2019). [PubMed: 31436582]
108. Bien SA et al. Strategies for enriching variant coverage in candidate disease loci on a multiethnic genotyping array. *PLoS ONE* 11, e0167758 (2016). [PubMed: 27973554]
109. Wang T et al. The Human Pangenome Project: a global resource to map genomic diversity. *Nature* 604, 437–446 (2022). [PubMed: 35444317]
110. Wong KHY et al. Towards a reference genome that captures global genetic diversity. *Nat. Commun.* 11, 5482 (2020). [PubMed: 33127893]
111. Long E et al. The case for increasing diversity in tissue-based functional genomics datasets to understand human disease susceptibility. *Nat. Commun.* 13, 2907 (2022). [PubMed: 35614099]
112. Kachuri L et al. Principles and methods for transferring polygenic risk scores across global populations. *Nat. Rev. Genet.* 25, 8–25 (2024). [PubMed: 37620596]
113. Lim SS & Drenkard C Understanding lupus disparities through a social determinants of health framework: the Georgians organized against lupus research cohort. *Rheum. Dis. Clin. North. Am.* 46, 613–621 (2020). [PubMed: 32981639]
114. All of Us Research Program Investigators. et al. The “All of Us” Research Program. *N. Engl. J. Med.* 381, 668–676 (2019). [PubMed: 31412182]
115. The National Genomics Research Library v5.1; <https://www.genomicsengland.co.uk/initiatives/100000-genomes-project/documentation> (Genomics England, 2020).
116. Cantor MN & Thorpe L Integrating data on social determinants of health into electronic health records. *Health Aff.* 37, 585–590 (2018).
117. Zhang L et al. Multidisciplinary care in patients with systemic lupus erythematosus: a randomized controlled trial in China. *Int. J. Clin. Pharm.* 41, 1247–1255 (2019). [PubMed: 31240553]
118. Fanouriakis A et al. Multidisciplinary approach to lupus nephritis: clinical pearls, pitfalls, and positioning of newly-approved agents. *Lupus* 32, 1155–1163 (2023). [PubMed: 37499240]
119. Suresh L, Malyavantham K, Shen L & Ambrus JL Jr Investigation of novel autoantibodies in Sjogren’s syndrome utilizing sera from the Sjogren’s international collaborative clinical alliance cohort. *BMC Ophthalmol.* 15, 38 (2015). [PubMed: 25881294]
120. Garthwaite K, Smith KE, Bambra C & Pearce J Desperately seeking reductions in health inequalities: perspectives of UK researchers on past, present and future directions in health inequalities research. *Sociol. Health Illn.* 38, 459–478 (2016). [PubMed: 27358991]
121. Collyer TA & Smith KE An atlas of health inequalities and health disparities research: “How is this all getting done in silos, and why? *Soc. Sci. Med.* 264, 113330 (2020). [PubMed: 32971486]
122. NIH-Office of Research on Women’s Health. Meet the 2023 EXACT-PLAN Award Recipients. <https://orwh.od.nih.gov/in-the-spotlight/all-articles/meet-2023-exact-plan-award-recipients> (2023).
123. Khan AT et al. Recommendations on the use and reporting of race, ethnicity, and ancestry in genetic research: experiences from the NHLBI TOPMed program. *Cell Genom* 2,100155 (2022). [PubMed: 36119389]
124. Carlson J, Henn BM, Al-Hindi DR & Ramachandran S Counter the weaponization of genetics research by extremists. *Nature* 610, 444–447 (2022). [PubMed: 36261568]
125. Schramowski P, Turan C, Andersen N, Rothkopf CA & Kersting K Large pre-trained language models contain human-like biases of what is right and wrong to do. *Nat. Mach. Intell.* 4, 258–268 (2022).
126. Bender EM, Gebru T, McMillan-Major A & Shmitchell S in: Proceedings of the 2021 ACM Conference on Fairness, Accountability, and Transparency. 610–623 (Association for Computing Machinery, Virtual Event, Canada, 2021).

127. Helget LN & Mikuls TR Environmental triggers of hyperuricemia and gout. *Rheum. Dis. Clin. North. Am.* 48, 891–906 (2022). [PubMed: 36333002]
128. Costenbader KH et al. Cigarette smoking and the risk of systemic lupus erythematosus: a meta-analysis. *Arthritis Rheum.* 50, 849–857 (2004). [PubMed: 15022327]
129. Freemer MM, King TE Jr & Criswell LA Association of smoking with dsDNA autoantibody production in systemic lupus erythematosus. *Ann. Rheum. Dis.* 65, 581–584 (2006). [PubMed: 16150789]
130. Takvorian SU, Merola JF & Costenbader KH Cigarette smoking, alcohol consumption and risk of systemic lupus erythematosus. *Lupus* 23, 537–544 (2014). [PubMed: 24763538]
131. Ekblom-Kullberg S et al. Smoking, disease activity, permanent damage and dsDNA autoantibody production in patients with systemic lupus erythematosus. *Rheumatol. Int.* 34, 341–345 (2014). [PubMed: 24170320]
132. Klareskog L, Padyukov L & Alfredsson L Smoking as a trigger for inflammatory rheumatic diseases. *Curr. Opin. Rheumatol* 19, 49–54 (2007). [PubMed: 17143096]
133. Forsyth C et al. The effects of the Mediterranean diet on rheumatoid arthritis prevention and treatment: a systematic review of human prospective studies. *Rheumatol. Int.* 38, 737–747 (2018). [PubMed: 29256100]
134. Pocovi-Gerardino G et al. Beneficial effect of Mediterranean diet on disease activity and cardiovascular risk in systemic lupus erythematosus patients: a cross-sectional study. *Rheumatology* 60, 160–169 (2021). [PubMed: 32594173]
135. Gwinnutt JM et al. 2021 EULAR recommendations regarding lifestyle behaviours and work participation to prevent progression of rheumatic and musculoskeletal diseases. *Ann. Rheum. Dis.* 82, 48–56 (2023). [PubMed: 35260387]
136. Metsios GS & Kitas GD Physical activity, exercise and rheumatoid arthritis: effectiveness, mechanisms and implementation. *Best. Pract. Res. Clin. Rheumatol.* 32, 669–682 (2018). [PubMed: 31203925]
137. Sieczkowska SM et al. Efficacy of home-based physical activity interventions in patients with autoimmune rheumatic diseases: a systematic review and meta-analysis. *Semin. Arthritis Rheum.* 51, 576–587 (2021). [PubMed: 33945907]
138. Blaess J et al. Benefits & risks of physical activity in patients with Systemic Lupus Erythematosus: a systematic review of the literature. *Semin. Arthritis Rheum.* 58, 152128 (2023). [PubMed: 36436314]
139. Wieczorek M et al. Smoking, alcohol consumption and disease-specific outcomes in rheumatic and musculoskeletal diseases (RMDs): systematic reviews informing the 2021 EULAR recommendations for lifestyle improvements in people with RMDs. *RMD Open* 8, e002170 (2022). [PubMed: 35351808]
140. Xu Y & Wu Q Prevalence trend and disparities in rheumatoid arthritis among US Adults, 2005–2018. *J. Clin. Med.* 10, 3289 (2021). [PubMed: 34362073]
141. Arkema EV & Cozier YC Sarcoidosis epidemiology: recent estimates of incidence, prevalence and risk factors. *Curr. Opin. Pulm. Med.* 26, 527–534 (2020). [PubMed: 32701677]
142. Izmirly PM et al. Prevalence of systemic lupus erythematosus in the United States: estimates from a meta-analysis of the Centers for Disease Control and Prevention National Lupus Registries. *Arthritis Rheumatol.* 73, 991–996 (2021). [PubMed: 33474834]
143. Leonardo NM & McNeil J Behcet’s disease: is there geographical variation? a review far from the silk road. *Int. J. Rheumatol.* 2015, 945262 (2015). [PubMed: 26798344]
144. Zhu W, Ayoub S, Morand E, Tillett W & Antony A The evolving demographics of participants in psoriatic arthritis phase III randomised controlled trials of b/tsDMARDs: a systematic review. *Semin. Arthritis Rheum.* 60, 152175 (2023). [PubMed: 36803867]
145. Izmirly PM et al. The incidence and prevalence of adult primary Sjögren’s syndrome in New York County. *Arthritis Care Res.* 71, 949–960 (2019).
146. Maldini C et al. Epidemiology of primary Sjögren’s syndrome in a French multiracial/multiethnic area. *Arthritis Care Res.* 66, 454–463 (2014).

147. Capelusnik D et al. Individual-level and country-level socio-economic factors and health outcomes in spondyloarthritis: analysis of the ASAS-perSpA study. *Rheumatology* 61, 2043–2053 (2022). [PubMed: 34387300]
148. Putrik P et al. Individual-level and country-level socioeconomic determinants of disease outcomes in SpA: multinational, cross-sectional study (ASAS-COMOSPA). *Ann. Rheum. Dis.* 78, 486–493 (2019). [PubMed: 30674477]
149. Takeshita J, Chau J, Duffin KC & Goel N Promoting diversity, equity, and inclusion for psoriatic diseases. *J. Rheumatol.* 49, 48–51 (2022). [PubMed: 35293335]

Key points

- Health disparities in rheumatic disease are well established and need addressing urgently.
- Currently, epidemiological and biological research exists in silos, which hampers our ability to elucidate the interplay and underlying molecular mechanisms by which environmental exposures yield biological changes.
- Poor diversity and inclusivity in research datasets, individual and structural barriers in access to research and care, inaccurate use of population descriptors, and research siloing limit equal and equitable precision medicine and health.
- Embracing ecological frameworks such as the biopsychosocial model will enable research that better accounts for the multi-faceted factors contributing to rheumatic disease prevalence and progression.
- The continued development of omics technologies and emerging large population-based registries offer great opportunities for identifying and alleviating health disparities.

Box 1 |**Examples of known health disparities in rheumatic diseases**

Overview of some documented differences in prevalence, incidence and severity across ten rheumatic diseases emphasizes the necessity of addressing these issues in research.

- Higher prevalence in African Americans: gout⁵¹, knee osteoarthritis⁵⁰, rheumatoid arthritis¹⁴⁰, sarcoidosis^{53,141}, systemic lupus erythematosus¹⁴² and systemic sclerosis⁵².
- Higher prevalence in Mediterranean countries, the Middle East, and Southeast Asia: Behçet's disease¹⁴³.
- Higher prevalence among European Americans: psoriatic arthritis¹⁴⁴.
- Higher prevalence among non-European populations: Sjögren's syndrome^{145,146}.
- Worse severity of disease for patients with lower socioeconomic status and/or countries with lower GDP: ankylosing spondylitis^{147,148}, psoriatic arthritis^{57,149}.

Box 2 |**Addressing obstacles to precision medicine equity**

To achieve equity in precision medicine, the research silos, social and structural barriers in access to research, care, behavioural or lifestyle options, and biomedical benefits must be addressed. The priorities with which to address these barriers include the following:

Structural issues

- Address delayed access to specialized clinical care
- Improve access to medical therapy and benefits from precision medicine (e.g. owing to health care coverage, or medication costs)
- Reform health care structures and pharmaceutical business models (e.g. drug-pricing models)
- Remove legal barriers (e.g. inadequate privacy and anti-discrimination protections for research participants, lack of health coverage and funding for follow-up care, failure to use law to ensure access to genomic medicine, and practices by research sponsors that tolerate and entrench disparities)
- Address the impacts of structural drivers of health, including racism
- Use knowledge to inform and incentivize sociopolitical reforms to reduce social inequalities and inequities
- Remove barriers to participation in research (e.g. geographical distance, mistrust of the health care system, language barriers) to increase inclusivity in research
- Consider precision medicine in a socioecological model, including environmental and structural factors that are beyond the individual's control

Diversity in backgrounds and expertise

- Foster collaborations in team science, utilizing international collaboration
- Support collaborations between biological and epidemiological scientists, academics and clinicians, and partnerships with institutions, community groups and patients
- Encourage commitment from biotechnology and pharma industries, health care systems and governments
- Include policymakers and legal experts to address legal barriers
- Address the conditions that structure power within research teams

Diversity in data resources

- Address the structural issues that foster the under-representation of some populations in basic and clinical research

- Improve diversity in population-based cohorts with validated diagnoses, clinical, exposure/environmental and omics data
- Support efforts to collect granular sociocultural and physical longitudinal exposures data and develop approaches to analysing their effects on molecular responses

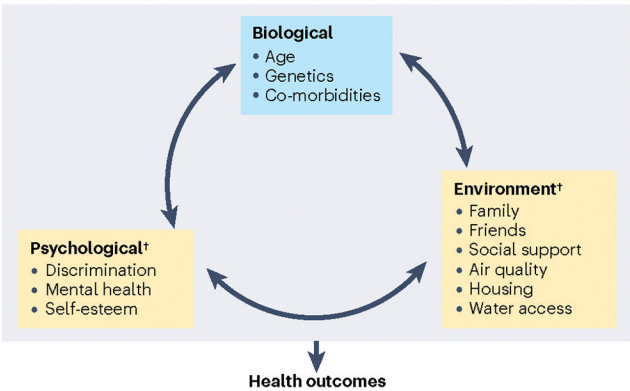
Infrastructure for research development

- Use multi-faceted frameworks for studying health disparities that include data for the multiple domains that contribute towards health disparities
- Adjust funding priorities

Disseminating research responsibly

- Engage in training to become aware of the ethical, legal and social implications of research and health disparities
- Assess and address individual biases
- Incorporate equity-related concerns in research and care
- Use clear, rigorous and respectful population labels that move away from crude and oversimplistic, discrete racial categories to describe exposures such as environmental determinants of health
- Acknowledge limitations of findings, such as explicit definitions of what environmental and/or social factors might not have been captured

a Biopsychosocial model



b Environmental determinants of health

Domain	Physical environment	Health care access	Biological	Chemical	Economic security and equality	Health behaviours	Social and community support
Subdomains	Air and water quality	Access	Animal dander	Air pollutants	Education access	Alcohol use	Conflict, crime and violence
	Climate and disasters	Affordability	Bacteria	Heavy metals	Education quality	Nutrition	Discrimination
	Energy/utilities access	Health system (for example, health workers per 1,000 people)	Cockroaches	Pesticides	Employment	Physical activity	Forced displacement/migration
	Healthy workplace		Mildew/mould		Food insecurity	Tobacco use	Gender equality
	Housing and safe house		Mites		Income inequality		Healthy ageing
	Road safety, traffic congestion and transportation systems		Pollen		Poverty		Incarceration
	Sanitation and hygiene		Viruses				Social capital, cohesion, connections and participation
	Urbanization						

Fig. 1 |. The biopsychosocial model and domains of environmental determinants of health.
a, The biopsychosocial model comprises biological, psychological and social factors; extensions of this model into an ecological model include other environmental factors.
†Sources of social determinants of health. **b**, Primary domains and subdomains of environmental determinants of health.

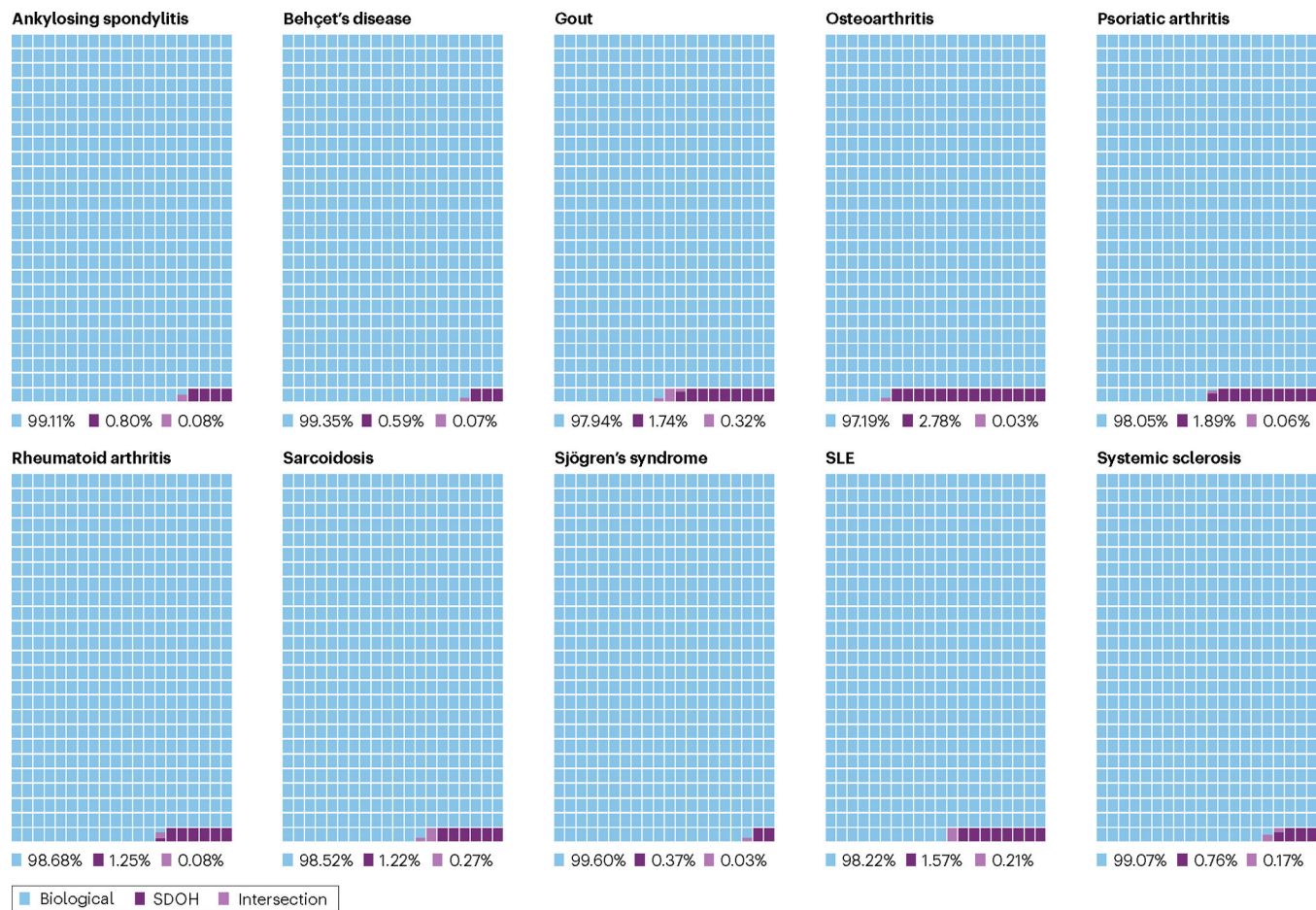


Fig. 2 |. Siloing of research in rheumatic diseases. Percentages of biological research, social determinants of health (SDOH) research and intersecting research were calculated based on a PubMed literature search. Percentages are visualized as rates of publishing per 500 papers. Icons are coloured according to research category and are rounded to the nearest quarter. Manuscripts spanning biological and SDOH topics account for <1% of publications across each of the evaluated diseases (see Supplementary Table 1 and Supplementary Fig. 1 for PubMed search criteria). SLE, systemic lupus erythematosus.

Table 1 |

Effect of environmental factors on rheumatic diseases

Environmental factors	Rheumatic disease	Epidemiological conclusions
Negative outcomes		
Low household income, poverty, unemployment	SLE and RA	Increased disease risk and severity ^{46–49}
	Gout and OA	Greater odds of developing disease ^{50,51}
	SSc and sarcoidosis	Worse outcomes ^{52–54}
Diet (purine rich)	Gout	Increased chance of experiencing flares ¹²⁷
Social deprivation and social vulnerability	OA, RA, ASp, sarcoidosis and SSc	Associated with rheumatic disease development ^{50,55,56}
Air quality and particulate exposures	RA	Worse disease activity and drug response ^{68–70}
Cigarette smoking	SLE	Worse disease activity ^{128–131}
	RA	Increased risk of developing disease ¹³²
Positive outcomes		
Social support, improved life satisfaction	SLE	Decreased depression and anxiety ^{59–62}
	RA	Improved depression, anxiety and quality of life ^{63–65}
Exiting poverty	SLE	Decreased disease damage ⁶⁷
Social support and spiritual well being	SSc	Improved life satisfaction ⁶⁶
Diet (Mediterranean)	SLE, RA	Improved disease activity ^{133,134}
Physical activity	SLE, gout, RA	Improved disease activity ^{135–139}

ASp, ankylosing spondylitis; OA, osteoarthritis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.