Gender-Diverse Inclusion in Immunological Research: Benefits to Science and Health

Hannah Peckham1,2*, Kate Webb3,4, Elizabeth C. Rosser1,2, Gary Butler5,6 and Coziana Ciurtin1,2

1 Centre for Adolescent Rheumatology Versus Arthritis at University College London (UCL), University College London Hospital (UCLH), Great Ormond Street Hospital (GOSH), London, United Kingdom, 2 Division of Medicine, Centre for Rheumatology Research, University College London (UCL), London, United Kingdom, 3 Department of Paediatric Rheumatology, School of Child and Adolescent Health, Red Cross War Memorial Children’s Hospital, University of Cape Town, Cape Town, South Africa, 4 Crick African Network, The Francis Crick Institute, London, United Kingdom, 5 Department of Paediatric and Adolescent Endocrinology, University College London Hospital (UCLH) and Great Ormond Street Institute of Child Health, University College London, London, United Kingdom, 6 Gender Identity Development Service (GIDS), Tavistock and Portman NHS Foundation Trust, London, United Kingdom

The differences between male and female immune systems are an under-researched field, ripe for discovery. This is evidenced by the stark sex biases seen in autoimmunity and infectious disease. Both the sex hormones (oestrogen and testosterone), as well as the sex chromosomes have been demonstrated to impact immune responses, in multiple ways. Historical shortcomings in reporting basic and clinical scientific findings in a sex-disaggregated manner have led not only to limited discovery of disease aetiology, but to potential inaccuracies in the estimation of the effects of diseases or interventions on females and gender-diverse groups. Here we propose not only that research subjects should include both cis-gender men and cis-gender women, but also transgender and gender-diverse people alongside them. The known interaction between the hormonal milieu and the sex chromosomes is inseparable in cis-gender human research, without the confounders of puberty and age. By inclusion of those pursuing hormonal affirmation of their gender identity- the individual and interactive investigation of hormones and chromosomes is permitted. Not only does this allow for a fine-tuned dissection of these individual effects, but it allows for discovery that is both pertinent and relevant to a far wider portion of the population. There is an unmet need for detailed treatment follow-up of the transgender community- little is known of the potential benefits and risks of hormonal supplementation on the immune system, nor indeed on many other health and disease outcomes. Our research team has pioneered the inclusion of gender-diverse persons in our basic research in adolescent autoimmune rheumatic diseases. We review here the many avenues that remain unexplored, and suggest ways in which other groups and teams can broaden their horizons and invest in a future for medicine that is both fruitful and inclusive.

Keywords: sex, gender, autoimmunity, sex hormones, sex chromosome, transgender
INTRODUCTION

The pertinent sex bias in the human immune system is a phenomenon that may never have come to light, were it not for significant policy changes that enforced the inclusion of female participants alongside males in medical research (1). Historically, clinical trials were conducted predominantly on male subjects only, or failed to discriminate between outcomes experienced by males vs. females (2). Justified by pragmatic reasons, predominantly healthy young males were recruited to avoid potential toxicity risks associated with pregnancy and breastfeeding, while excluding more mature patients of both sexes to decrease the risk of concomitant comorbidity. Little differed in basic scientific research, where male-only mouse sexes to decrease the risk of concomitant comorbidity. Little differed in basic scientific research, where male-only mouse models mitigated the outcome variability potentially resulting from the menstrual cycle or pregnancy, and most in vitro human work failed to report the sex of the cell lines used (3). This approach is not only inaccurate in answering research questions relevant to humans, irrespective of sex and gender, but is also potentially harmful in underestimating the effects of interventions on females and other gender-diverse groups. Although medical understanding and subsequent research study design have advanced significantly in recent years, this chronic failure to recognise the importance of sex as a key biological variable has by no means been fully overcome. Anecdotally, in attempting to collect data on global COVID-19 morbidity and mortality between the sexes, it was notable how few countries or local authorities were reliably disaggregating their outcome statistics according to patients’ sex, even at later stages of the pandemic (4). Sophisticated national platforms detailed deaths according to geographical regions, age groups and occupational categories, but frequently neglected to mention sex. Our meta-analysis (5), alongside several other studies (6–8), showed a significant male bias in severe outcomes and deaths from SARS-CoV-2; a pattern mirrored in the vast majority of infectious diseases (9–11) and variously suggested to relate to sex hormone levels (12–14). The enhanced ability of the female immune system to clear invading pathogens is further supported by its ability to mount generally stronger responses to most vaccinations (15–17). For example, in adults given the seasonal Trivalent Inactivated Influenza Vaccine, female responses to a half-dose were comparable to those of males given a full-dose (18). The inverse of this is of course the female predisposition to developing autoimmune disorders associated with a hyper-active immune system, such as systemic lupus erythematosus (SLE), where the male:female ratio is estimated at 4–13:1, according to different studies (19–28).

Both hormonal and chromosomal factors are suggested to contribute to immunological sex differences. Oestradiol is broadly thought of as immunostimulatory, with testosterone having a more regulatory effect (29), though both have demonstrated either capability, as reviewed elsewhere (30–33). Meanwhile the X chromosome encodes the most immune-related genes of any chromosome (34) such as TLR7 [toll like receptor, responsible for sensing viral and endogenous nucleic acids to trigger release of type 1 interferons, and implicated in extrafollicular B cell class switch recombination (35)], CD40-L [co-stimulatory T cell molecule, essential for B cell class switching (36)], FoxP3 [controls regulatory T cells (37)] and CXCR3 [chemokine receptor, recruits effector T cells to sites of inflammation (38)]. This is highlighted by the abundance of X-linked immune disorders such as immunodysregulation polyendocrinopathy enteropathy X-linked (or IPEX) syndrome, X-linked agammaglobulinemia and Wiskott Aldrich Syndrome, which are associated with cellular and humoral immune deficiencies and increased risk of infections from childhood (39). Several immune genes on the X chromosome may escape the X-inactivation of one chromosome in 46,XX individuals, and thus be bi-allelically expressed, potentially resulting in altered immune regulation (40–43). Whilst studies have sought to investigate the contributions of hormonal and/or chromosomal influences on the immune response, it is recognised that it is a complex nexus and mutual interaction of the two that ultimately leads to such notable sex biases in infection and autoimmunity. With this in mind, this review seeks to highlight the importance of including subjects of both sexes, as well as transgender people in immunological research, to enable evaluation of sex-biased clinical outcomes and provide benefit to our understanding of the biology of the immune system with relevance for both science and health.

GENDER IDENTITIES AND PHYSICAL PHENOTYPES

For the majority of the population, the terms sex and gender describe the binary categories of “cisgender male” and “cisgender female”; with experienced gender matching the sex registered at birth, which is itself based upon simple observation of the genitalia of the newborn baby. Frequently assimilated within the category of “other,” however, are a multitude of gender identities and physical phenotypes. By “transgender” we refer broadly to those whose experienced gender identity does not match that in which they were registered at birth. Thus, trans-males, are registered female at birth, typically carry a 46,XX chromosomal background, and may pursue virilisation via testosterone treatment and/or oestradiol blockade. Trans-females, are registered male at birth, typically of 46,XY chromosomal background, and may pursue gender-affirming oestradiol treatment and/or testosterone blockade (44). Specific treatment pathways and medications recommended by the Endocrine Society (45) are summarised in Figure 1. A third main category are those who are non-binary/gender fluid (not identifying exclusively and/or permanently as either gender); some of whom may seek hormonal blockade via treatments such as the gonadotropin releasing hormone analogs (GnRHs), or specific hormonal blockades. There is also the category of differences/disorders of sex development (previously known as ‘intersex’), where people may have physical characteristics of both sexes (gonadal structures, genitalia) and this umbrella term also includes those with karyotype variations of sex development such as Klinefelter syndrome [47,XXY] and Turner syndrome [45,X] (46). Lastly but by no means exhaustively are those classified as
“agender”- not identifying with any gender at all. Many other gender-related groupings exist, beyond the scope of this review, but we have included here the main categories pertinent to immunological research.

To refer again to international COVID statistics, even fewer countries reported outcomes in those who were not cisgender. In some countries, the catch-all ‘other’ category was reported alongside cisgender males and females; but this was representative of so many diverse groups that granular analyses of differential gender-related outcomes could not be possible. Such is the case for the vast majority of outcome reporting in health and disease, suggesting that better characterisation of populations pertaining to self-reported gender is warranted. In the United Kingdom alone, referrals to the NHS young people’s Gender Identity Development Service (GIDS) have increased by over 2000% in the last 10 years (47); this represents a growing proportion of society who are frequently not even adequately recognised in statistics, let alone included in basic science or relevant clinical research. Here we examine potential ways in which inclusion of a broader spectrum of gender groups can improve our scientific understanding of the pathogenesis of both infectious diseases and autoimmune disorders, as well as providing potentially pertinent clinical information for under-represented groups and the physicians involved in their care.

The multitude of gender-related social factors that may contribute to increased vulnerability to different medical conditions are beyond the scope of this paper and reviewed elsewhere (48). However, the physiological impact of a person’s sex chromosomal makeup combined with their hormonal milieu (be this endogenous or medically supplemented) is what we propose to be an important focus of future research. In cis-gender people, the contributions of sex chromosomes and hormones are inextricably linked. We know both to be of significance, but researchers currently are able to separate these factors to examine how they interact and separately contribute only in animal models and in vitro research. By inclusion of trans or gender-diverse persons pursuing hormonal affirmation of their gender, we are able to investigate the effects of hormonal manipulation on the immune system in healthy individuals of a wide age range (usually older than 16 in the United Kingdom).

**SEX BIAS IN THE EPIDEMIOLOGY AND OUTCOMES OF AUTOIMMUNE RHEUMATIC DISEASES**

The majority of autoimmune rheumatic disorders (ARDs) affect cis-females in greater number than cis-males, as is the case with SLE, Sjögren’s syndrome (SS) (49), scleroderma (SSc) (50) and rheumatoid arthritis (RA) (51). SLE predominantly affects females of child-bearing age, with incidence pre-puberty significantly lower (52) and pregnancy associated with increased flares in patients with recently active disease (53, 54). Taken together, these epidemiological observations strongly suggest a role for the sex hormones in disease pathogenesis. However, juvenile rheumatic diseases, defined as having onset before the age of 16–18 years depending on phenotype, such as juvenile idiopathic arthritis (JIA), juvenile lupus (JSLE), juvenile Sjögren’s syndrome (JSS) and juvenile dermatomyositis (JDM) also exhibit sex bias, but this is less prominent than in their corresponding adult-onset phenotypes (55). JIA, for example, has no significant sex bias overall as an umbrella term, but different disease sub-types are characterised by different age at onset and sex-predominance: e.g., Enthesitis Related Arthritis (ERA) affects predominantly boys and has onset around puberty, while subtypes oligo- and poly-arthritis are more common in pre-pubertal and post-pubertal girls, respectively (56). As pre-pubertal cis-boys and cis-girls have similar serum sex hormone levels, a potential role for the sex chromosomes in the disease pathogenesis is thus also supported.

Several studies have investigated the effect of hormonal medications in SLE, where one might expect to see exacerbation of disease upon use of the oral contraceptive (OC), or hormone replacement therapy with oestriadiol (HRT) given to alleviate menopausal symptoms. Commonly cited is the Nurse Health Study, which followed thousands of ciswomen, and reported an elevated relative risk for the development of SLE of 1.9 for women who had ever used hormonal OC (57) and of 2.1 in post-menopausal women who had ever used (HRT) (58). Although hormonal treatments have been purported to cause flares in SLE in older studies (59), recent literature has demonstrated little to no impact of OC usage on mild to moderate SLE, with the potential for unplanned pregnancies deemed a more significant risk for patients than OC use (60, 61). Several studies have demonstrated reduced androgen levels in SLE patients (62, 63), and this has been suggested to play a role in disease development or severity. Therein, the use of various forms of androgen as therapeutic agents has been tested in several incidences – with some trials showing mild efficacy (64–68) while others showed no difference from placebo (69). Thus, the current literature on in vivo manipulation of hormones does not provide a conclusive picture. Several case studies (70–77) detail the development of autoimmunity in trans-females upon commencement of gender-affirming oestriadiol treatment, or the improvement of symptoms when taking gender-affirming testosterone (78). However, one cannot infer causality from these instances, nor can individual case studies be extrapolated to the wider population. Inclusion of trans people in bigger cohort studies on autoimmunity development is thus strongly supported – whether the increased relative risk seen in post-menopausal cis-females on HRT would be the same or similar in trans-women with an XY chromosomal background is yet unknown.

Although the majority of autoimmune diseases are characterised by female bias, there is evidence that type 1 diabetes mellitus and Crohn’s disease are characterised by a male predominance, irrespective of age at onset (79, 80). Additionally, some conditions have differential disease phenotypes according to sex, which has implications in disease recognition and epidemiological data collection. This is the case with spondyloarthritis (81), which had been considered a male-predominant disease for many decades before evidence about a different clinical presentation and delays in diagnosing females with spondyloarthritis emerged (82). Further, certain treatments may be more efficacious in one sex compared to the other [recently reviewed extensively by Klein and Morgan (83)], e.g., TNF inhibitors tend to work better for males with RA.
immune activation pathways, such as specific cell populations or pro-inflammatory pathways, where both sex chromosomal and hormonal elements have been separately suggested to be of influence is an area with great scope for new discovery. Work from our lab, published in 2019 (103), pioneered the inclusion of gender-diverse cohorts to address questions relevant to SLE, using a cohort of healthy trans- \( (n = 13 \text{ male}, 7 \text{ female}) \) and cisgender \( (n = 48 \text{ male}, 51 \text{ female}) \) young volunteers, alongside individuals with Turner Syndrome \( (n = 9) \), who are missing an X chromosome \( (45,X) \). Young transgender healthy controls were recruited from the University College London Hospital GIDS and treatment pathways are shown in Figure 1. Production of the antiviral cytokine family known as type 1 interferons (IFN)- predominantly by plasmacytoid dendritic cells (pDC)- is known to contribute significantly to the pathogenesis of both SLE and JSLE. We demonstrated that pDC from healthy cis-females produced more T1 IFN in response to TLR-7 signalling than pDC from cis-males, even before puberty. Using our inclusive volunteer cohort, we were additionally able to show that this related to X chromosome dosage and serum testosterone concentration, in a manner that was dependent upon the number of X chromosomes present. Overall, we showed that both factors were associated not just individually, but also interactively with the T1 IFN response.

More recently, we used a similar cohort \( (n = 17 \text{ cis-male}; 22 \text{ cis-female}; 10 \text{ trans-male and 10 trans-female}) \) to examine the effects of sex and hormones on regulatory and responder CD4 + T cells (Tregs and Tresps, respectively) \( (104) \). Sex differences in Tregs are well-reported \( (105–109) \), and we firstly confirmed the observation that healthy cis-males have higher levels of Tregs compared to Tresps than cis-females both pre- and post-puberty. We then demonstrated that the ability of cis-male Tregs to suppress the division of Tresps was significantly enhanced compared to that of cis-female Tregs, supporting the concept of a pro-inflammatory phenotype in females that could contribute to autoimmunity. Then, using RNA sequencing (RNAseq), we found a significant number of differentially expressed genes (DEGs) in sorted Tregs from cis-males compared to females. Using our transgender healthy controls, we observed significant differences in related immune pathways following hormone treatment, demonstrating the potential for both oestradiol and testosterone to impact Tregs at a transcriptional level, even at the early stages of their treatment.

The COVID-19 pandemic has prompted several interesting studies on sex differences in viral responses, and how these translate into clinical outcomes. Takahashi et al. \( (8) \) demonstrated a more robust T cell response in females with the disease, compared to males- with poor T cell responses associated with a worse disease trajectory in males. Meanwhile males had higher levels of innate inflammatory cytokines, but higher levels of these in females were associated with more severe outcomes. Supporting these findings, Liu et al. \( (110) \) compared transcriptional differences in healthy males and females, demonstrating that males had higher expression of proinflammatory cytokines and chemokines, which they hypothesise may contribute to the ‘cytokine storm’ that is detrimental in COVID-19 pathogenesis. Females in this study were found to have higher expression of IFN genes, supporting

### IMPACT OF AGE, PUBERTY AND MENOPAUSE ON AUTOIMMUNITY

Throughout the various life stages from infancy to old age, the immune system is also subject to great change \( (87, 88) \), and these changes are known to differ between cisgender males and females \( (89) \). The ageing immune system is a growing area of research, but less is known specifically about the immune changes that may occur during/after puberty and menopause. The coincidence of the average age of onset of several juvenile rheumatic diseases \( (90) \) with the average age of puberty onset \( (91) \) suggests that it is not merely the maturation process itself that alters one's immune system, but that the rise in sex hormone levels seen in puberty is also involved. Our systematic review of the bidirectional relationship between puberty and autoimmune rheumatic disorders demonstrated how poorly these relationships are documented in the literature, but highlighted the differences in disease outcome in those with onset pre- vs. post-puberty \( (92) \) and symptomatic differences have been noted between different age groups of SLE patients \( (93) \), with adolescent onset JSLE noted for its greater severity \( (94, 95) \). In the case of menopause, RA \( (96) \) and SSc \( (97) \) both have their peak incidence in the over 50 age bracket. SLE has classically been considered to have its peak incidence within the childbearing years in females, but a 10-year incidence study of United Kingdom patients found the peak onset to be between 50 and 54 years in females and 70–74 in males \( (98) \), and this was supported by two other shorter studies \( (21, 99) \). However, these studies were of predominantly white populations, and in studies including black \( (100) \), Arab \( (101) \) and American Indian \( (102) \) patients, younger ages of peak onset between 30.4 and 39.2 have been observed. It is unclear exactly why this might be, but this highlights the complexity of sex-based influences on the immune system, which may interact with both age- and ethnicity-related factors to give rise to autoimmunity. With the inclusion of transgender subjects of different ages and pubertal/menopausal stages among basic and clinical research, these factors could be separated out, and the impact of sex be examined without the confounders of immunosenescence and ethnically inherited risk factors.

### DIFFERENTIAL EFFECT OF SEX DETERMINANTS ON IMMUNE ACTIVATION PATHWAYS

The investigation of the impact of sex-determinants on certain immune activation pathways, such as specific cell populations
what is already known about the sex bias in IFN production in health and in autoimmunity. These data demonstrate a clear link between sexual dimorphism in the immunological systems that serve to protect us, that may also lead to damage in the context of an autoimmune disease. Inclusion of trans and gender-diverse cohorts in infection response studies, is thus equally warranted alongside those in autoimmunity.

There remain myriad of cell types and mechanisms that have been identified as potentially influenced by sex hormones or chromosomes, thus meriting \textit{in vivo} interrogation. In addition to the further work necessitated on pDCs, the T1 IFN pathway, and Tregs/Tresps, obvious suggestions for future research directions (based on preliminary evidence of sex hormonal/chromosomal effect in animal or non-diverse cohorts) are B cells and antibody/autoantibody production (111–120), B regulatory (Breg) cells (121), CD4 T cells (116, 122–124), and specific T helper subsets (89, 125–131), CD8 cytotoxic T cells (122, 132–135), dendritic cells (136–140), Natural Killer (NK) cells (116, 141–145), neutrophils (146–149), monocytes (150) and macrophages (149, 151, 152). Table 1 summarises a selection of notable effects of sex determinants on immune processes and cell types known to be relevant to autoimmune rheumatic disease—this is by no means an exhaustive review of the literature, and many extensive reviews are available (89, 182, 183). As a field in its relative infancy, there remain so many avenues ripe for gender-disaggregated interrogation and scintillating project proposals.

**UNANSWERED QUESTIONS AND FUTURE DIRECTIONS**

There is an unmet need for better understanding of the long-term outcomes of sex hormone manipulation on the health of trans and gender-diverse people. This includes the effects of gender-affirming treatment on responses to natural and vaccine immunisations, on bone and muscle health, as well

---

**FIGURE 1** | Treatment pathway for gender incongruence, as recommended by the Endocrine Society (42). Treatment is prescribed on a case-by-case basis, based on individual country guidelines. This flowchart outlines the most commonly pursued routes. NB: Parenteral oestradiol not currently used in Europe. MHP: Mental health professional; GnRHs, Gonadotropin releasing hormone analogs; LH, Luteinising hormone; FSH, Follicle stimulating hormone; IM, Intramuscular; SC, Subcutaneous.
**TABLE 1 |** Summary of notable immune system elements known to be regulated by sex determinants and their relevance to autoimmune rheumatic disease.

| Immune cells | Cis-female | Cis-male | Relevance to autoimmune rheumatic diseases (ARD) |
|--------------|------------|----------|-------------------------------------------------|
| **B cells**  | Oestrogens shown to: alter the threshold for B cell apoptosis/activation (112); increase capacity for class-switch recombination (114, 115, 117, 113, 119). | Androgens act via GPR174 to divert B cells from germinal centre formation and subsequent class-switching (120). Testosterone regulates BAFF – important in survival of autoreactive B cells (118). | Production of autoantibodies central to pathogenesis of many ARDs. |
| **Immunoglobulins** | Higher plasma Ig levels in females (111, 118). | – | Multiple roles across ARDs (153, 154). |
| **CD8 T cells** | Lower cell frequency but higher cytotoxic capacity in females (135). | Higher cell frequencies in males (122, 123, 132). | Subset imbalance (155) and functional abnormalities in SLE (156). Pathogenic role in JIA uveitis (157). |
| **CD4 T cells** | Higher cell frequencies in females (116, 122, 123, 132). | – | Role in SLE disease manifestations (159) and IL-17 in RA (160). Initiation of SS (161). Th17 axis implicated in AS pathology (162). |
| **Treg subset** | Androgens enhance female CD4 + T cell FoxP3 expression in vitro (159). | Male Tregs had greater suppressive ability (104). | SS initiation (Th1) and progression (Th2) Psianou et al. (161) Th1:Th2 imbalance in RA (163). |
| **Th17 subset** | Oestrogens both stimulatory (126, 127) and suppressive (128) of proliferation and IL-17 production. Activation via ERα enhances Th17 response, via ERα suppresses (130). | Frequency of IL-17A and Th17 cells increased in males with AS compared to females with AS (129). | – |
| **Th1 subset** | Oestrogen and progesterone decrease Th1:Th2 and Th17:Th2 cytokine production ratios (131). Male V female Th1 or Th2 predominance varies, reviewed in (169). | – | SS initiation (Th1) and progression (Th2) Psianou et al. (161) Th1:Th2 imbalance in RA (163). |
| **Th2 subset** | Macrophage phagocytic activity higher in females (148). | Testosterone increases monocyte counts in men (149). | Inflammatory damage to cartilage and bone in RA etc. (164). Defects in phagocytosis and clearance of cellular debris in SLE (165). Presentation of self-antigen. |
| **Macrophages and Monocytes** | | Higher levels in hypogonadal males inversely correlated to testosterone levels (140). | IFN production prominent role in SLE pathogenesis (167). Release of proinflammatory cytokines and NET formation externalises autoantigens (168). |
| **Dendritic Cells (DC)** | E2 enhanced ability of DCs to activate CD4 + Th cells in vitro (136, 138). | – | Presentation of self-antigen. |
| **Plasmacytoid Dendritic Cells (pDC)** | More activated in females and produce more IFN-α (103, 166). | – | IFN production prominent role in SLE pathogenesis (167). |
| **Neutrophils** | Phagocytic activity higher in females (146). Oestrogens and progesterone can affect lifespan (147) and numbers increased during luteal phase of menstruation and in pregnancy (148). | Testosterone increases counts in men (149). | Release of proinflammatory cytokines and NET formation externalises autoantigens (168). |
| **Natural Killer Cells (NK)** | | Increased CNS NK inflammation in males vs. females in ALS mouse model - NK depletion benefitted females but not males (145). | Cytotoxicity in inflammation and role in immunoregulation/immune homeostasis (169). |
| **Cytokines and Immune Mediators** | | | |
| **Type 1 Interferons** | IFN-α production higher in female cells post TLR stimulation (103, 170). | Testosterone correlates with IFN-α independently from X chromosome (103). | Prominent role in SLE pathogenesis (167). Inflammatory role in SLE, SS, SSc and dermatomyositis (171). |
| **Type 2 Interferons** | E2 treatment in mice increased DC production of IFN-γ (138). | IFN-γ higher in stimulated lymphocyte supernatant from males (170). | Breg and IL-10 role in SLE, RA and SSc (173). |
| **IL-10** | Higher production in stimulated lymphocyte supernatant from females (170). | Higher production in males and correlates with testosterone (172). | – |
| **Microbiota** | Bi-directional relationship between hormones and microbiota, with immune impact (174, 175). | | Known impact of microbiota on rheumatic disorders (176). |
| **Transcriptional Differences** | | | |
| **Macrophages (MF)** | Higher expression of MF IFN-stimulated genes in female mice, with sig. bias in antiviral response genes (177). | – | IFN role in SLE, SS, SSc, RA and dermatomyositis (178). |
| **CD8 Cytotoxic cells** | Greater toxicity post-stimulation in female cells: antiviral and inflammatory gene expression increased, many with oestrogen response elements in their promoters (134). | – | Multiple roles across ARDs (155, 156). |
| **AIRE (autocrine regulator)** | Oestrogens inhibit (179). | Androgens enhance (180). | Necessary for self-tolerance induction in the thymus (181). |

**BAFF, B cell Activating Factor; Ig, Immunoglobulins; ERα, Oestrogen Receptor Alpha; ERβ, Oestrogen Receptor Beta; AS, Ankylosing Spondylitis; CNS, Central Nervous System; ALS, Amyotrophic Lateral Sclerosis; IFN, Interferon; TLR, Toll-like Receptor.**
as their impact on mental health and quality of life, before moving into investigating infective and autoimmune risk in these populations. Without accurate gender classifications in population studies, these relevant outcomes cannot be studied. There are many specific questions which need answering in relation to the impact of sex determinants on immune system functions, in particular around exposure to and timings of exposure to sex hormones. We do not know if the length of exposure to/blockade of a particular sex hormone is different from the physiological sex hormone fluctuations, especially those related to menstruation, pregnancy, or early stages of puberty/ menopause. There is no research into the impact of age at which a person is first exposed to (or begins blocking) sex hormones on their risk of infections, autoimmunity, or other adverse health outcomes. Our group identified a significant impact of sex hormones in driving a pro-atherogenic lipid profile in healthy cis- and trans-male adolescents post-puberty (184). Therefore, investigating the impact of sex-affirming hormone therapy on the cardio-vascular risk of trans people has a clear clinical rationale. Further research is needed to investigate the effects of lifetime exposure to higher exogenous oestrogen or androgen therapies, especially in the context of potential reversibility and dose-dependent long-term effects. In some countries, young people are able to commence puberty blockade and gender-affirming sex hormones prior to the commencement of their natural puberty. Meanwhile in the United Kingdom, only those aged 16 + and thus likely already post-pubertal can legally be consented to start on gender-affirming hormone treatments. Others still, may not access treatment until much later into adulthood. It is important to establish whether outcomes (immunological or otherwise) would be similar or different in these groups, when their hormonal transitions have commenced at such widespread life stages. Furthermore, it is possible that different routes of hormone administration (oral, patch, gel, IM, SC.) and dosages of these may impact the systems of the human body differently. Innovative clinical trial study design, including volunteers of all gender categories, across various age ranges is required to be able to examine the relative importance of sex hormone exposure at different stages of life, against both sex chromosomal backgrounds, on various interventions or health and disease outcomes. In addition, the inclusion of subjects with altered sex chromosomal complement (such as Klinefelter and Turner syndromes) could provide suitable controls for these studies aiming to tease out the distinct effects of various sex chromosome determinants.

First steps would be establishing national and international registries with associated biological sample repositories capturing patients of various gender categories, sex chromosomal

![Adaptations and Study Set-up](https://www.frontiersin.org)

- Establish links between hospital/outpatient clinic GIDS and research labs
- Trans community involvement and engagement
- LGBTQ+ competency training for all staff involved. Language and terminology used to be reviewed regularly.

![Basic Science Research Themes](https://www.frontiersin.org)

- Investigate effects of Hx blockade/replacement on:
  - Immune cell phenotype & function
  - Inflammatory mediators
  - Genomics
  - Transcriptomics
  - Proteomics
  - Metabolomics
  - Microbiome

![Clinical Research Themes](https://www.frontiersin.org)

- Investigate effects of Hx blockade/replacement on risk for/outcomes:
  - Vaccination
  - Autoimmunity
  - Infectious disease
  - Cancer
  - Allergy/asthma
  - General physical health e.g. bone, muscle, growth, CVD
  - Mental health, quality of life etc.

**FIGURE 2** | Suggested adaptations to facilitate future research encompassing trans and gender-diverse individuals, and key research pathways proposed. Hx, Hormones; GnRHα, Gonadotropin Releasing Hormone Agonists (“Blockers”); CVD, Cardiovascular Disease.
backgrounds and demographic diversity to enable long-term follow-up. A number of social barriers exist, well-documented in the United States, that prevent the trans population from accessing healthcare and thus participating in research (185). Thus, it is important for such registries to be set up with advice and input from transgender charities and organisations such as WPATH (World Professional Association for Transgender Health) on how to overcome these barriers. This should include ensuring that all health professionals and researchers involved are trained in LGBTQ + cultural competency (186), so that all elements of study design - from language used on questionnaires, to subtlety when approaching people for recruitment- are optimised to help participants feel secure and respected. Further, recruitment must extend beyond private healthcare patients, encompassing public healthcare clinics as well as community support groups, in order to capture the true breadth of the trans population. Hospital and clinic record databases must be updated in order to capture gender definitions and associated medications more accurately, and reference ranges for clinical and laboratory tests need to be reviewed and established for gender-diverse people, as it is highly likely that they may differ from those appropriate for cis persons (187). If these changes were made across the world, they would not only facilitate far more impactful retrospective review of outcomes, but would vastly improve the lives and healthcare of transgender persons, who have tolerated systems that weren’t designed to accommodate them for far too long. In Figure 2, we propose several streams of research, both clinical and immunological, as starting points for future projects. Researchers and clinicians should join forces to give people of all gender identities a voice and create opportunities for their involvement in clinical data collection and research. As more countries develop their gender identity services, and adapt to the changes outlined above, we look forward to seeing the results from further large studies such as 2021 Michelson Prize recipient Dr. Camila Consiglio’s multi-parameter analysis of the effect of testosterone treatment on the immune systems of trans-men at the Karolinska Institutet, Sweden (188), and that of Professor Guy T’Sjoen’s ENIGI consortium across Ghent, Oslo, Florence, and Amsterdam (189, 190), where long-term follow-up of participants pursuing hormonal gender affirmation will provide us with a wealth of information, pertinent to everyone – not just those it is convenient to study.

CONCLUDING REMARKS

We advocate that research should celebrate gender diversity and be as inclusive as possible to ensure that it is relevant to human society as a whole. We can only hope that in coming years, more labs and clinical teams will join us in the interrogation of sex determinants as biological variables. As personalised medicine becomes an increasingly viable and beneficial approach to healthcare, it is research like this that will be equipped to inform and steer innovation in the appropriate direction.

DISCLAIMER

Gender-related terminology is continually evolving, and terms vary in their usage between individuals and between groups across the world. Language and definitions used throughout this article have been adapted from the Gender Identity Research and Education Society (GIRES) website at time of writing (191) – we have made every effort to be inclusive, but acknowledge that these may not capture the preferences and experiences of all.

AUTHOR CONTRIBUTIONS

CC, GB, and HP contributed to conception of the review. HP wrote the first draft of the manuscript and designed the figures. CC, GB, KW, and ER wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

FUNDING

This work was supported by as grants from the NIHR UCLH Biomedical Research Centre (Grant Nos: BRC772/III/E/J/101350 and BRC773/III/CC/101350), Lupus United Kingdom and was performed within the Centre for Adolescent Rheumatology Versus Arthritis at UCL, UCLH, and GOSH supported by grants from Versus Arthritis (21593 and 2016). HP was supported by a Versus Arthritis Studentship to CC (22203). KW was supported by the Crick African Network which receives its funding from the United Kingdom’s Global Challenges Research Fund (MR/P028071/1), and by the Francis Crick Institute which receives its core funding from Cancer Research United Kingdom (FC1001647), the United Kingdom Medical Research Council (FC1001647), and the Wellcome Trust (FC1001647). ER was supported by a Medical Research Foundation Lupus Fellowship to ER (MRF-057-0001-RG-ROSS-C0797). The funders of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

ACKNOWLEDGMENTS

We thank to Hannah-Louise Hayman (University of Glasgow), for her thoughtful comments and insight on the manuscript.

REFERENCES

1. Clayton JA. Studying both sexes: a guiding principle for biomedicine. FASEB J. (2016) 30:519–24. doi: 10.1096/fj.15-279554

2. Geller SE, Koch AR, Roesch P, Filut A, Hallgren E, Carnes M. The more things change, the more they stay the same: a study to evaluate compliance with inclusion and assessment of women and minorities in randomized controlled trials. Acad Med. (2018) 93:630–5. doi: 10.1097/ACM.0000000000002027
21. Jonsson H, Nived O, Sturfelt G, Silman A. Estimating the incidence of systemic lupus erythematosus in Birmingham. *Arthritis Rheum.* (1995) 38:551–8. doi: 10.1002/art.1780380415

22. Dhindsa S, Zhang N, McPhaul MJ, Wu Z, Ghoshal AK, Erlich EC, et al. Sex differences in susceptibility to viral infection. *J Immunol.* (2020) 204:181–7. doi: 10.1016/j.jimmunol.2020.01.068

23. Nossent JC. Systemic lupus erythematosus in the Arctic region of Norway. *J Rheumatol.* (2001) 28:539–46.

24. Petri M. Epidemiology of systemic lupus erythematosus. *Best Pract Res Clin Rheumatol.* (2002) 16:847–58. doi: 10.1016/S1744-5563(02)00025-X

25. Trigunaite A, Dimo J, Jørgensen TN. Suppressive effects of androgens on the immune system. *Cell Immunol.* (2015) 294:87–94. doi: 10.1016/j.cellimm.2015.02.004

26. Johnson AE, Gordon C, Palmer RG, Bacon PA. The prevalence and incidence of systemic lupus erythematosus in Baltimore, Maryland, 1970-1977. *Arthritis Rheum.* (1978) 21:1162–7. doi: 10.1002/art.1780210415
66. Chang DM, Lanv JL, Lin HY, Luo SF. Dehydroepiandrosterone treatment of women with mild-to-moderate systemic lupus erythematosus: a multicenter randomized, double-blind, placebo-controlled trial. *Arthritis Rheum.* (2002) 46:2924–7. doi: 10.1002/art.10615

67. Petri MA, Meese PJ, Merrill JT, Lahita RG, Iannini MJ, Yocum DE, et al. Effects of prasterone on disease activity and symptoms in women with active systemic lupus erythematous. *Arthritis Rheum.* (2004) 50:2858–68. doi: 10.1002/art.20427

68. Gordon C, Wallace DJ, Shinada S, Kalunian KC, Forbess L, Braunstein GD, et al. Testosterone patches in the management of patients with mild/moderate systemic lupus erythematosus. *Rheumatology* (2008) 47:334–8. doi: 10.1093/rheumatology/kem342

69. Tzourou OM, Quismorio FP. Rheumatoid arthritis in a male transsexual. *J Rheumatol.* (1985) 12:640–1.

70. Santos-Ocampo AS. New onset systemic lupus erythematosus in a transgender man: possible role of feminizing sex hormones. *J Clin Rheumatol.* (2007) 13:29–30. doi: 10.1097/01.rhu.0000256169.50087.ad

71. Zandman-Goddard G, Solomon M, Barzilai A, Shoefield Y. Lupus erythematosus tumidus induced by sex reassignment surgery. *J Rheumatol.* (2007) 34:1938–40.

72. Chan KL, Mok CC. Development of systemic lupus erythematosus in a male-to-female transsexual: the role of sex hormones revisited. *Lupus.* (2013) 22:1399–402. doi: 10.1177/0961203313500550

73. Pakpoor J, Wotton CJ, Schmiere K, Giovanni G, Goldacre MJ. Gender identity disorders and multiple sclerosis risk: a national record-linkage study. *Mult Scler.* (2016) 22:1759–62. doi: 10.1177/1352458515627205

74. Campochiaro C, Host LV, Ong VH, Denton C. Development of systemic sclerosis in transgender females: a case series and review of the literature. *Clin Exp Rheumatol.* (2018) 36:550–2.

75. Pontes LT, Camilo DT, De Bortoli MR, Santos RS, Luchi WM. New-onset lupus nephritis after male-to-female sex reassignment. *Lupus.* (2018) 27:2166–9. doi: 10.1177/0961203318800571

76. Hill BG, Hodge B, Missricia R. Lupus nephritis in a transgender woman on cross-sex hormone therapy: a case for the role of oestrogen in systemic lupus erythematosus. *Lupus.* (2020) 29:1807–10. doi: 10.1177/1423190420963732

77. Ocon A, Peredo-Wende R, Kremer JM, Bhat BD. Significant improvement of subacute cutaneous lupus after testosterone therapy in a female-to-male transgender subject. *Lupus.* (2018) 27:347–8. doi: 10.1177/0961203317734921

78. Ostman J, Lönneberg G, Arqvist HJ, Błomé G, Bolinder J, Schnell AE, et al. Gender differences and temporal variation in the incidence of type 1 diabetes: results of 8012 cases in the nationwide Diabetes Incidence Study in Sweden 1983-2002. *J Intern Med.* (2008) 263:386–94. doi: 10.1111/j.1365-2966.2007.04906.x

79. Ishige T, Tomomasa T, Takebayashi T, Asakura K, Watanabe M, Suzuki T, et al. Inflammatory bowel disease in children: epidemiological analysis of the nationwide IBD registry in Japan. *J Gastroenterol.* (2010) 45:911–7. doi: 10.1007/s00535-010-0223-7

80. Jovani V, Blasco-Blasco M, Pascual E, Ruiz-Cantero MT. Challenges to conquer from the gender perspective in medicine: the case of spondyloarthritis. *PLoS One.* (2018) 13:e0205751.

81. Roussou E, Sultana S. Spondyloarthritis in women: differences in disease onset, clinical presentation, and Bath Ankylosing Spondylitis Disease Activity and Functional indices (BASDAI and BASFI) between men and women with spondyloarthritides. *Clin Rheumatol.* (2011) 30:121–7. doi: 10.1007/s10067-010-1581-5

82. Klein SL, Morgan R. The impact of sex and gender on immunotherapy outcomes. *Biol Sex Differ.* (2020) 11:1–10. doi: 10.1186/s13239-020-00301-y

83. Jayakumar K, Norton S, Dixey J, James D, Gough A, Williams P, et al. Sustained clinical remission in rheumatoid arthritis: prevalence and outcome rates. *Rheumatology.* (2012) 51:169–75. doi: 10.1093/rheumatology/ker250

84. Souto A, Maneiro JR, Gómez-Reino JJ. Rate of discontinuation and drug survival of biologic therapies in rheumatoid arthritis: a systematic review and meta-analysis of drug registries and health care databases. *Rheumatology* (2016) 55:523–34. doi: 10.1093/rheumatology/kev374
123. Uppal SS, Verma S, Dhot PS. Normal values of CD4 and CD8 lymphocyte subsets in healthy adult men and the effects of age, ethnicity, and smoking. Cytom Part B Clin Cytom. (2003) 52B:32–6. doi: 10.1002/cyto.b.10011

124. Sancho-Walters S, Macal M, Grishina I, Nagy L, Gouart L, Coolidge K, et al. Sex differences matter in the gut: effect on mucosal immune activation and inflammation. Biol Sex Differ. (2013) 4:1–12. doi: 10.1186/2404-6140-4-10

125. Buckner JH. Mechanisms of impaired regulation by CD4(+)CD25(+)FOXP3(+) regulatory T cells in human autoimmune diseases. Nat Rev Immunol. (2010) 10:849–59. doi: 10.1038/nri2889

126. Smith S, Nigabahnn J, McCarthy E, Coffey B, Mahony R, Byrne JC, et al. Estrogen receptor α regulates tripartite motif-containing protein 21 expression, contributing to dysregulated cytokine production in systemic lupus erythematosus. Arthritis Rheumatol (Hoboken, NJ). (2014) 66:163–72. doi: 10.1002/art.38187

127. Newcomb DC, Cephus JY, Boswell MG, Fahrenholz JM, Langley EW, Chen R-Y, Fan Y-M, Zhang Q, Liu S, Li Q, Ke G-L, et al. Estradiol inhibits up-regulation of Th17-type responses. J Immunol. (2015) 194:4019–28. doi: 10.4049/jimmunol.1400806

128. Gracey E, Yao Y, Green B, Qaiyum Z, Baglaenko Y, Lin A, et al. Sexual dimorphism in the Th17 signature of ankylosing spondylitis. Arthritis Rheumatol. (2016) 68:679–89. doi: 10.1002/art.39464

129. Qin J, Li L, Jin Q, Guo D, Liu M, Fan C, et al. Estrogen receptor β activation stimulates the development of experimental autoimmune thyroiditis through up-regulation of Th17-type responses. Clin Immunol. (2018) 190:41–52. doi: 10.1016/j.clim.2018.02.006

130. AbdullHussain G, Azzieh F, Makhseed M, Raghupathy R, Chen R-Y, Fan Y-M, Zhang Q, Liu S, Li Q, Ke G-L, et al. Estradiol inhibits Th17 cell differentiation through inhibition of RORγT transcription by recruiting the ERα/REα complex to estrogen response elements of the RORγT promoter. J Immunol. (2015) 194:4019–28. doi: 10.4049/jimmunol.1400806

131. Butts CL, Shukair SA, Duncan J, et al. Estrogen preferentially recruits the ERα complex to estrogen response elements of the Th17 signature of ankylosing spondylitis. J Immunol. (2015) 194:4019–28. doi: 10.4049/jimmunol.1400806

132. Lisse IM, Aaby P, Whitlett H, Jensen H, Engelmann M, Christensen LB. T-cell modulation of TLR3- and TLR4-mediated dendritic cell maturation and inflammation. J Immunopharmacol. (2015) 41:315–26. doi: 10.1016/j.jimp.2015.05.046

133. Lü FX, Abel K, Ma Z, Rourke T, Lu D, Torten J, et al. The strength of B cell activation in healthy Indian adults and the effects of sex, age, ethnicity, and smoking. Cytom Part B Clin Cytom. (2012) 81:254–62. doi: 10.1002/cyto.b.21056

134. Murdock BJ, Famie JP, Pechuck CE, Auhe KD, Mendelson FE, Pernon CH, et al. NK cells associate with ALs in a sex- and age-dependent manner. JCI Insight. (2021) 6:e147129.

135. Spitza J, Gender differences in some host defense mechanisms. Lupus. (1999) 8:3830–10. doi: 10.1177/09612339990080101

136. Paharkova-Vatchkova V, Maldonado R, Kovats S. Estrogen preferentially regulates tripartite motif-containing protein 21 expression, contributing to dysregulated cytokine production in systemic lupus erythematosus. J Immunol. (2010) 185:4525–34. doi: 10.4049/jimmunol.1001155

137. Walecki M, Eisel F, Klug J, Baal N, Paradowska-Dogan A, Wahle E, et al. Clinical and immunological parameters of Sjögren’s syndrome. J Immunol. (2005) 174:2362–8. doi: 10.4049/jimmunol.17402362.2012.02712.x

138. Hou J, Wu FZ. Effect of sex hormones on NK and ADCC activity of mice. Int J Immunopharmacol. (1988) 10:15–22. doi: 10.1016/0191-9914(88)90145-2

139. Vouel G, Shukair SA, Ben-Eliyahu S. The effects of sex, menstrual cycle, and oral contraceptives on the number and activity of natural killer cells. Gynecol Oncol. (2001) 81:254–62. doi: 10.1006/gyno.2001.6153

140. Agostino P, Milano S, Barbera C, Di Bella G, La Rosa M, Ferlazzo V, et al. Sex hormones modulate inflammatory mediators produced by macrophages. Ann N Y Acad Sci. (1999) 876:426–9. doi: 10.1111/j.1749-6632.1999.tb07667.x

141. Jones LA, Kreem S, Shweash M, Paul A, Alexander J, Roberts CW. Selective inhibition of CD8+ T cells in autoimmunity. Curr Opin Immunol. (2005) 17:624–31. doi: 10.1016/j.coi.2005.09.014

142. Corrales JJ, Almeida M, Cordero M, Martín-Martín L, Méndez C, Miralles JA, et al. Enhanced immunological response by dendritic cells in male hypogonadism. Eur J Clin Invest. (2012) 42:1205–12. doi: 10.1111/j.1365-2362.2012.02712.x

143. Menzies FM, Henriquez FL, Alexander J, Roberts CW. Selective inhibition and augmentation of alternative macrophage activation by progesterone. J Immunol. (2011) 134:281–91. doi: 10.1111/j.1365-2567.2011.03488.x

144. Walter U, Santamaría P, CD8+ T cells in autoimmunity. Curr Opin Immunol. (2005) 17:624–31. doi: 10.1016/j.coi.2005.09.014

145. Collier JL, Weiss SA, Pauken KE, Sen DR, Sharpe AH. Not-so-opposite ends of the spectrum: CD8+ T cell dysfunction across chronic infection, cancer and autoimmunity. Nat Immunol. (2021) 22:809–19. doi: 10.1038/s41590-021-00949-7

146. He J, Zhang X, Ye W, Sun X, Chen Y, Deng J, et al. Low-dose interleukin-2 treatment selectively modulates CD4+ T cell subsets in patients with systemic lupus erythematosus. Nat Med. (2016) 22:991–3. doi: 10.1038/nm.4148

147. Gao X, Liu L, Min X, Ya S, Zhao M. Non-Coding RNAs in CD4+ T cells: new insights into the pathogenesis of systemic lupus erythematosus. Front Immunol. (2020) 11:568. doi: 10.3389/fimmu.2020.00568

148. Clarke SL, Sen ES, Ramanav A, Juvenile idiopathic arthritis-associated uveitis. Pediatr Rheumatol. (2016) 14:1–11. doi: 10.1186/s12969-016-0088-2

149. Galecki M, Eisel F, Klug J, Baal N, Paradowska-Dogan A, Wahle E, et al. Androgen receptor regulates Foxp3 expression in CD4+ CD25+ Foxp3 + regulatory T-cells. Mol Biol Cell. (2015) 26:2845–57. doi: 10.1091/mbc.E14-08-1323

150. Kim BJ, Kim YH, Lee S, Han JH, Lee SY, Jeong J, et al. Otological aspects of NLRP3-related autoinflammatory disorder focusing on the responsiveness to anakinra. Rheumatol. (2021) 60:1523–32. doi: 10.1093/rheumatology/keaa511

151. Llabrés E, The IL-23–IL-17 axis in inflammatory arthritis. Nat Rev Rheumatol. (2015) 11:415–29. doi: 10.1038/nrrheum.2015.53

152. Pianou K, Nagapoulos I, Papanastasios AD, de Lastic AL, Rodri M, Pantipade, et al. Clinical and immunological parameters of Sjögren’s syndrome. Autoimmun Rev. (2018) 17:1053–64. doi: 10.1016/j.autrev.2018.05.005
171. Pollard KM, Cauvi DM, Toomey CB, Morris KV, Kono DH. Interferon-

179. Dragin N, Bismuth J, Cizeron-Clairac G, Biferi MG, Berthault C, Serraf

177. Gal-Oz ST, Maier B, Yoshida H, Seddu K, Elbaz N, Czysz C, et al.

178. Muskardin TLW, Niewold TB. Type I interferon in rheumatic diseases.

176. Konig MF. The microbiome in autoimmune rheumatic disease.

Best Pract Res

175. Rizzetto L, Fava F, Tuohy KM, Selmi C. Connecting the immune system,

Clin Rheumatol. (2020) 34:101473. doi: 10.1016/j.berh.2019.101473

Pubmed Central

173. Sakkas LI, Daoussis D, Mavropoulos A, Liossis SN, Bogdanos DP. Regulatory

174. Udalova IA, Mantovani A, Feldmann M. Macrophage heterogeneity in the

168. Gupta S, Kaplan MJ. The role of neutrophils and NETosis in autoimmune

169. Zitti B, Bryceson YT. Natural killer cells in inflammation and autoimmunity.

166. Berghöfer B, Frommer T, Haley G, Fink L, Bein G, Hackstein H. TLR7

165. Li Y, Lee PY, Reeves WH. Monocyte and macrophage abnormalities in

164. Islander U, Jochems C, Lagerquist MK, Forsblad-d’Elia H, Carlsten H.

163. Islander U, Jochems C, Lagerquist MK, Forsblad-d’Elia H, Carlsten H.

FEMS Microbiol Rev. (2015) 39:509–21. doi: 10.1093/femsre/fuu010

172. Torcia MG, Nencioni L, Clemente AM, Civitelli L, Celestino I, Limongi D, et al. Sex differences in the response to viral infections: TLR8 and TLR9 ligand stimulation induce higher IL10 production in males. PLoS One. (2012) 7:e39983. doi: 10.1371/journal.pone.0039983

170. Pollard KM, Cauvi DM, Toomey CB, Morris KV, Kono DH. Interferon-γ and systemic autoimmunity. Discov Med. (2013) 16:123.

167. Neuman H, Debelius JW, Knight R, Koren O. Microbial endocrinology: the interplay between the microbiota and the endocrine system. FEMS Microbiol Rev. (2015) 39:509–21. doi: 10.1093/femsre/fuu010

175. Rizzetto L, Fava F, Tuohy KM, Selmi C. Connecting the immune system, systemic chronic inflammation and the gut microbiome: the role of sex. J Autoimmun. (2018) 92:12–34. doi: 10.1016/j.jaut.2018.05.008

174. Gal-Oz ST, Maier B, Yoshida H, Seddu K, Elbaz N, Czysz C, et al. ImmGen report: sexual dimorphism in the immune system transcriptome. Nat Commun. (2019) 10:1–14. doi: 10.1038/s41467-019-12348-6

176. Konig MF. The microbiome in autoimmune rheumatic disease. Best Pract Res Clin Rheumatol. (2020) 34:101473. doi: 10.1016/j.berh.2019.101473

177. Gal-Oz ST, Maier B, Yoshida H, Seddu K, Elbaz N, Czysz C, et al. ImmGen report: sexual dimorphism in the immune system transcriptome. Nat Commun. (2019) 10:1–14. doi: 10.1038/s41467-019-12348-6

178. Muskardin TLW, Niewold TB. Type I interferon in rheumatic diseases. Nat Rev Rheumatol. (2018) 14:214. doi: 10.1038/nrrheum.2018.31

179. Dragin N, Bismuth J, Cizeron-Clairac G, Biferi MG, Berthault C, Serraf A, et al. Estrogen-mediated downregulation of AIRE influences sexual dimorphism in autoimmune diseases. J Clin Invest. (2016) 126:1525–37. doi: 10.1172/JCI81894

180. Zhu ML, Bakhru P, Conley B, Nelson JS, Free M, Martin A, et al. Sex bias in CNS autoimmune disease mediated by androgen control of autoimmune regulator. Nat Commun. (2016) 7:11350. doi: 10.1038/ncomms11350

181. Perniola R. Twenty years of AIRE. Front Immunol. (2018) 9:98. doi: 10.3389/fimmu.2018.00098

182. Jallion S, Berthenet K, Garlanda C. Sexual dimorphism in innate immunity. Clin Rev Allergy Immunol. (2019) 56:308–21.

183. Cutolo M, Straub RH. Sex steroids and autoimmune rheumatic diseases: state of the art. Nat Rev Rheumatol. (2010) 6:1628–44. doi: 10.1038/s41584-020-0503-4

184. Robinson GA, Peng J, Peckham H, Radziszewska A, Butler G, Pineda-Torra I, et al. Sex hormones drive changes in lipoprotein metabolism. iScience. (2021) 24:103257. doi: 10.1016/j.isci.2021.103257

185. Redcay A, Bergquist K, Luquet W. On the basis of gender: a medical-legal review of barri eres for healthcare for transgender and gender-expansive patients. Soc Work Public Health. (2021) 36:615–7. doi: 10.1080/19371918.2021.1942378

186. Radix A, Maingi S. LGBT cultural competence and interventions to help oncology nurses and other health care providers. Semin Oncol Nurs. (2018) 34:80–9. doi: 10.1016/j.son neph.2017.12.005

187. Greene DN, McPherson GW, Rongtisch J, Imborek KL, Schmidt RL, Humble RM, et al. Hematology reference intervals for transgender adults on stable hormone therapy. Clin Chim Acta. (2019) 492:84–90. doi: 10.1016/j.cca.2019.02.011

188. Chapman J. 2021 Michelson Prize Recipient Dr. Camila Consiglio Explores Differences Between the Sexes to Develop More Targeted Vaccines. Michelson Medical Research Foundation. (2021). Available online at: https://www.michelsonmedicalresearch.org/news/2021-michelson-prize-recipient-dr-camila-consiglio (accessed May 9, 2022).

189. Reardon S. The largest study involving transgender people is providing long-sought insights about their health. Nature. (2019) 568:446–9. doi: 10.1038/d41586-019-01237-z

190. Dekker MJHJ, Wierckx K, Van Caenegem E, Klaver M, Kreukels BP, Elaut E, et al. A European network for the investigation of gender incongruence: endocrine part. J Sex Med. (2016) 13:994–9. doi: 10.1016/j.jsxm.2016.03.371

191. GIRES. Terminology. (2022). Available online at: https://www.gires.org.uk/resources/terminology/ (accessed February 14, 2022).

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Peckham, Webb, Rosser, Butler and Curtin. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.