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Out of balance: the role of evolutionary mismatches in the sex disparity in autoimmune disease

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ABSTRACT

Over the past century autoimmune disease incidence has increased rapidly in (post-) industrialised, affluent societies, suggesting that changes in ecology and lifestyle are driving this development. Epidemiological studies show that (i) 80% of autoimmune disease patients are female, (ii) autoimmune diseases co-occur more often in women, and (iii) the incidence of some autoimmune diseases is increasing faster in women than in men. The female preponderance in autoimmunity is most pronounced between puberty and menopause, suggesting that diverging sex hormone levels during the reproductive years are implicated in autoimmune disease development. Using an evolutionary perspective, we build on the hypotheses that female immunity is cyclical in menstruating species and that natural selection shaped the female immune system to optimise the implantation and gestation of a semi-allogeneic foetus. We propose that cyclical immunomodulation and female immune tolerance mechanisms are currently out of balance because of a mismatch between the conditions under which they evolved and (post-)industrialised, affluent lifestyles. We suggest that current changes in autoimmune disease prevalence may be caused by increases in lifetime exposure to cyclical immunomodulation and ovarian hormone exposure, reduced immune challenges, increased reproductive lifespan, changed reproductive patterns, and enhanced positive energy balance associated with (post-)industrialised, affluent lifestyles. We discuss proximate mechanisms by which oestrogen and progesterone influence tolerance induction and immunomodulation, and review the effect of the menstrual cycle, pregnancy, and contraceptive use on autoimmune disease incidence and symptoms.

Introduction

Over the past 150 years, life expectancy in (post-)industrialised, affluent societies has increased concurrently with advances in public health, medicine, nutrition, and sanitation [1]. Whilst incidence of infectious diseases has consequently declined, the prevalence of degenerative and chronic diseases, detrimental to quality of life and long-term health, is increasing [2]. After cardiovascular disease and cancer, autoimmune diseases are now the most common disease category in the United States, with 5–8% of the population affected [3]. Autoimmune disorders are caused by an immune response erroneously launched against an individual's own body because of the loss of immune non-reactivity, also known as immune **tolerance**, for self-antigens [4]. More than eighty autoimmune diseases have been identified and the worldwide prevalence is estimated at approximately 4.5% [5]. In recent decades autoimmune disease incidence has rapidly increased in (post-) industrialised, affluent societies, at rates of between 3.7 and 7.1% annually [6], suggesting that contemporary changes in our ecology ecolo and lifestyle are driving this trend.

As the category of autoimmune disease encompasses a wide range of disorders, resulting from diverse aetiologies and affecting a variety of bodily systems, there are only few epidemiological studies that have aggregated autoimmune disease incidence. However, when looking at these reports it is striking that (i.) approximately four out of every five autoimmune disease patients is female [3,7], (ii.) the incidence of some inflammatory autoimmune diseases, most notably multiple sclerosis (MS), is increasing faster in females than males [8], and (iii.) the co-occurrence of several autoimmune diseases in one individual is more

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common among women than men [9]. Furthermore, when comparing autoimmune diseases first presenting themselves in early adulthood to those with a childhood onset, an increase in the female propensity to develop autoimmune diseases can be noticed for some disorders following the pubertal transition (Fig. 1) [10,11], whilst an opposite shift in the sex disparity is seen following menopause when the female: male incidence gap narrows again for some but not all autoimmune diseases [10,12,13] (see Fig. 2).

Evolutionary medicine suggests that the transition to life in an evolutionary novel environment associated with a(post-)industrialised, affluent lifestyle may have significant repercussions for psychological and physiological functioning as conditions in these contexts are fundamentally different from those in which we evolved, causing an evolutionary **mismatch** [14]. Making use of Tinbergen's four questions in biology, covering both **ultimate** and **proximate explanations** for health and disease, evolutionary medicine allows for the integration of insights into the developmental plasticity and evolutionary significance of biological traits with the **proximate** molecular mechanisms underlying them [15–17]. Such an approach sheds new light on the biological paradox that women are on the one hand more likely to experience a breakdown of **tolerance** to specific self-antigens in autoimmune disease, whereas they must also be able to tolerate the presence of a **semi-allogeneic** foetus during nine months of gestation in order to reproduce successfully. Sir Peter Medawar, one of the pioneers of transplantation science, was the first to suggest that research into **immunomodulation** and **tolerance** during pregnancy may enhance our understanding of the **tolerance** mechanisms that also play a role in the development of autoimmune disease [18]. He suggested that in response to pregnancy, which he likened to the implantation of an allograft, mothers dampen down their immune responses indiscriminately to prevent immunological rejection of the offspring. Although research has shown that pregnant mothers are not systemically immunosuppressed nor the foetus immunologically inert [19], understanding **immunomodulation** during pregnancy may still offer novel insights into the propensity of women to develop autoimmune diseases during their lifetime more often than men. Explanatory Box 1 gives an overview of all **proximate mechanisms** that may predispose and trigger autoimmune disease in women and that have been previously proposed to underlie the sex disparity in autoimmune disease.

We propose that increased lifetime exposure to reproductive hormones and number of menstrual cycles might alter **central** and **peripheral tolerance** mechanisms and contribute to an increase in autoimmune disease incidence in women living in (post-) industrialised, affluent contexts. Natri *et al.* [20] have previously hypothesised that as a

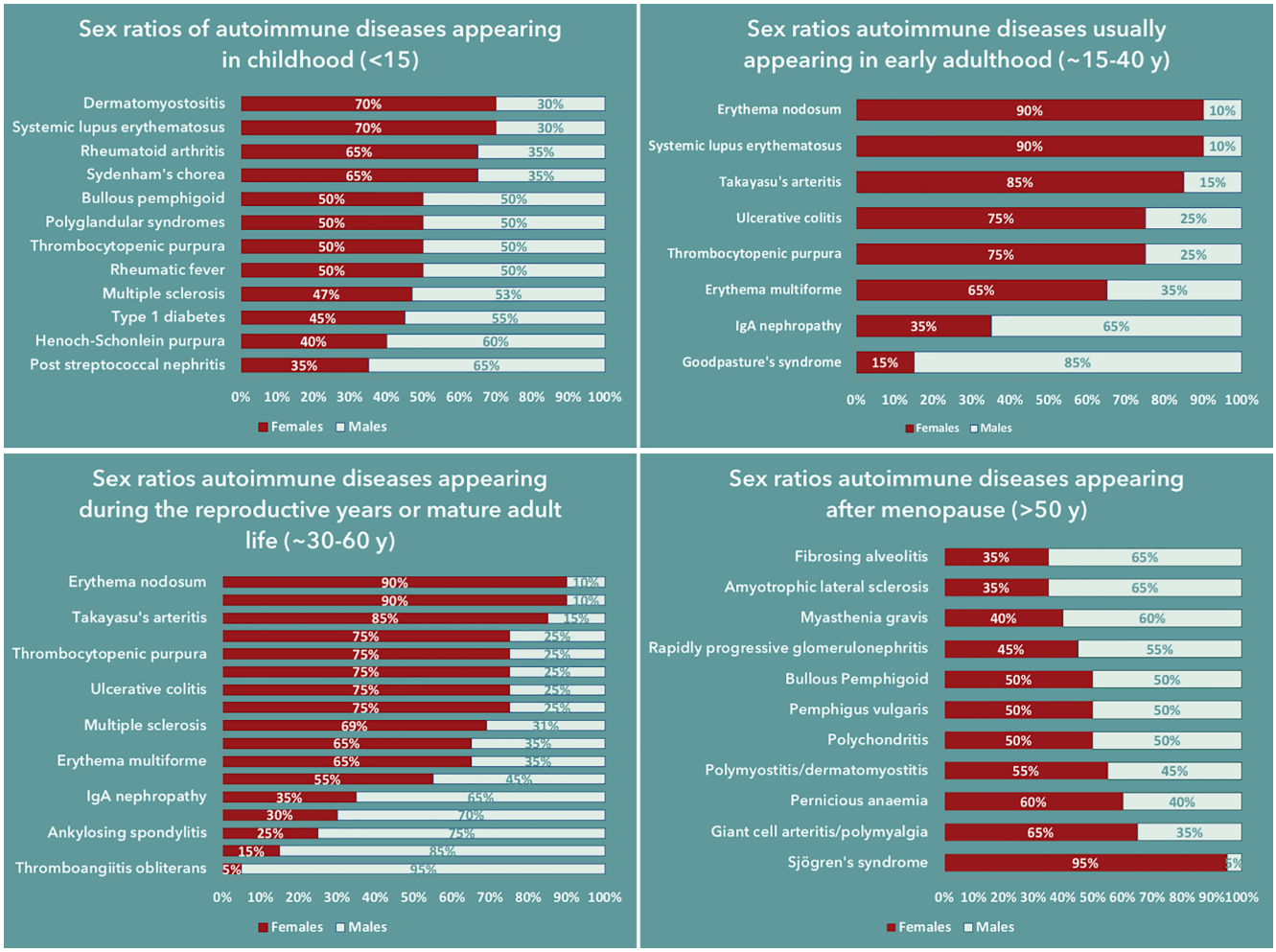

Fig. 1. Sex ratios in autoimmune diseases incidence during childhood versus those that are likely to appear during early adulthood, the reproductive years or after menopause. N.B. that some of the autoimmune diseases with childhood onset have an infectious aetiology. Interestingly autoimmune disorders that appear in early adulthood and more often occur in women, also more frequently co-occur with other autoimmune diseases. Comparing the last graph on the bottom left with the first graph on the top right, one can see that after menopause the sex disparity in autoimmune disease incidence is more similar to that seen before the onset of the reproductive years. Please note that in the publication by Beeson [10]a these graphs are based on, teenagers up to age 15 were counted as 'children'. Considering that most girls undergo menarche before age 15, this might skew the graphs' ability to demonstrate the influence of the reproductive transition itself on autoimmune incidence. The graphs are a visualisation of data taken from Beeson [10]; MS data from Chitnis [11].

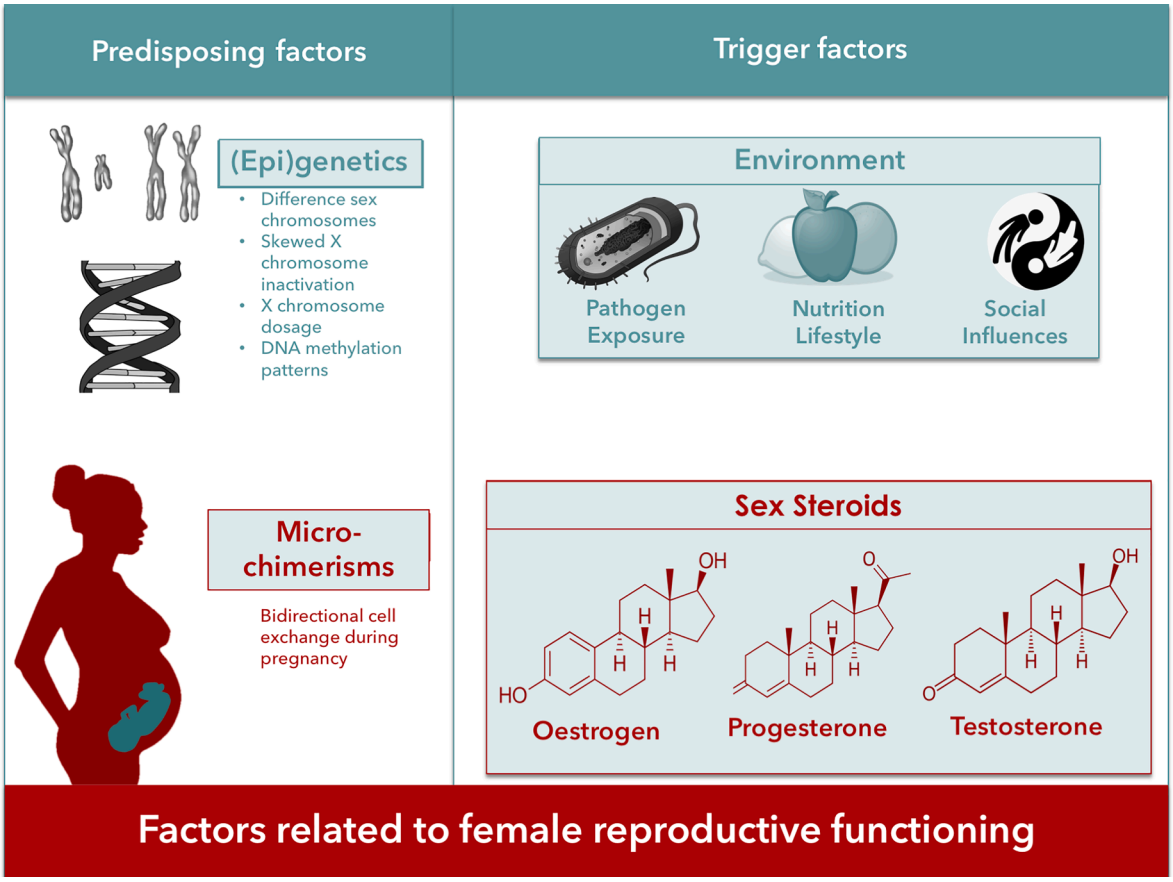

Fig. 2. An overview of the different proximate mechanisms that have been proposed to explain the difference in autoimmune prevalence between men and women. We have reorganised these proximate explanations to reflect the distinction between predisposing and triggering factors for autoimmunity. In red are factors that are directly related to female reproductive functioning. Drawing inspired by Quintero *et al.* [155], Anaya [9], and Rubtsova *et al.* [156].

result of natural selection on pregnancy and invasive placentation, evolved sex differences in gene content and dosage might contribute to sex-specific immune modulation and underlie the observed sexual dimorphism in autoimmune disease and cancer rates [20]. Alvergne and Högqvist Tabor [152] have additionally pointed out the cyclical nature of female health, and suggested that the effects of menstrual cycle on the immune function need to be considered when studying autoimmune disease from an evolutionary perspective. Building on these propositions, we hypothesise that cyclical immunomodulation through female sex hormones contributes to the observed sex disparity in autoimmune disease incidence and symptoms. Using an evolutionary ecology framework, we discuss the effect of ovarian steroids on the regulation of the adaptive immune system at different stages of female reproductive lifespan. We also discuss how recent alterations in reproductive patterns, lifestyle, and the consequent increase in the lifetime exposure to ovarian steroid hormones, might have exacerbated the sex disparity in autoimmune disease in recent decades. We furthermore predict that when populations start adopting a (post-)industrialised, affluent lifestyle characterised by energetic affluence [21,22], the sex disparity in autoimmune diseases may further increase. We specifically review the pathways by which sex hormones modulate lymphocyte development and differentiation during menstrual cycle and pregnancy, discussing the role of puberty and menopause in sex difference in autoimmune disease incidence. By doing so we provide evidence for the hypothesis that reproductive hormone levels shape autoimmune disease incidence and symptoms during a female's reproductive lifespan by modulating tolerance mechanisms and immunoregulation during the menstrual cycle and pregnancy. Finally, we highlight some relevant findings regarding the influence of ecological pressures on ovarian hormones in women, based on which we suggest new avenues for autoimmune disease research.

Evolutionary mismatches and the prevalence of autoimmune disorders

We propose that the observed increase in autoimmune disease prevalence and patterns might be caused by a mismatch between the ecological conditions in which immune **tolerance** and cyclical **immunomodulation** mechanisms originally evolved in and modern (post-) industrialised, affluent lifestyles (Fig. 3). Here, we summarise these mismatches, which may lead to higher lifetime exposure to ovarian steroids and cyclical immunomodulation and may contribute to the observed increased incidence in autoimmune diseases amongst women in (post-)industrialised, affluent contexts, focussing on: 1) increased reproductive lifespan, 2) changing reproductive patterns, 3) fewer immune challenges, 4) positive energy balance.

Increased reproductive lifespan

Currently, girls living in (post-)industrialised, affluent environments often undergo menarche earlier than previous generations [23,24], and are therefore exposed to the cyclical changes in **tolerance** and **immunomodulation** for a longer period of time. In (post-)industrial, affluent contexts, age of first menstruation has declined dramatically over the past two centuries concurrent with improved quality of early life environments and decreases in infant mortality rates [25]. This, along with a potential upward secular trend in age of menopause, has increased female reproductive lifespan [26]. Girls that undergo menarche before age

Explanatory Box 1
An overview of proximate mechanisms that may contribute to the sex disparity in autoimmunity

A wide range of molecular mechanisms have been identified that may contribute to a higher autoimmune disease prevalence in women than in men, which can be subdivided in both predisposing and triggering factors (Figure 2). Whereas predisposing factors contribute to the development of immune cells that aberrantly recognise self-antigens as foreign in the first place, trigger factors may cause the subsequent activation of these **autoreactive** immune cells. For example, skewed X-chromosome activation in women may cause **autoreactive T-cells** for certain X-linked genes escape tolerance induction processes during thymic development [155], whereas differential exposure to environmental-, dietary-, social-, and stress-related factors, may subsequently play a role in triggering autoimmune disease [17,156]. Several predisposing and triggering factors also directly relate to female reproductive functioning. For example, the bidirectional exchange of cells during pregnancy may predispose women to develop autoimmunity following pregnancy when immune responses are launched to remove foreign foetal cells (microchimerisms) from the body [157,158], whilst men and women also display different immune profiles during the reproductive years under the influence of pregnancy and sex hormones more generally. Research has furthermore shown that women exhibit stronger **humoral** and **cellular immune responses** than men as the 'female' sex hormones oestrogen and progesterone favour the survival of the adaptive immune system's **B-cells** and **T-helper- (Th) cells** [11,54,145,146]. Using an evolutionary medicine approach, we evaluate the effects of the ovarian steroids oestrogen and progesterone on the adaptive immune system's tolerance mechanisms in particular, describing pathways by which sex hormones influence the development and symptoms of autoimmune disease in women during the reproductive years.

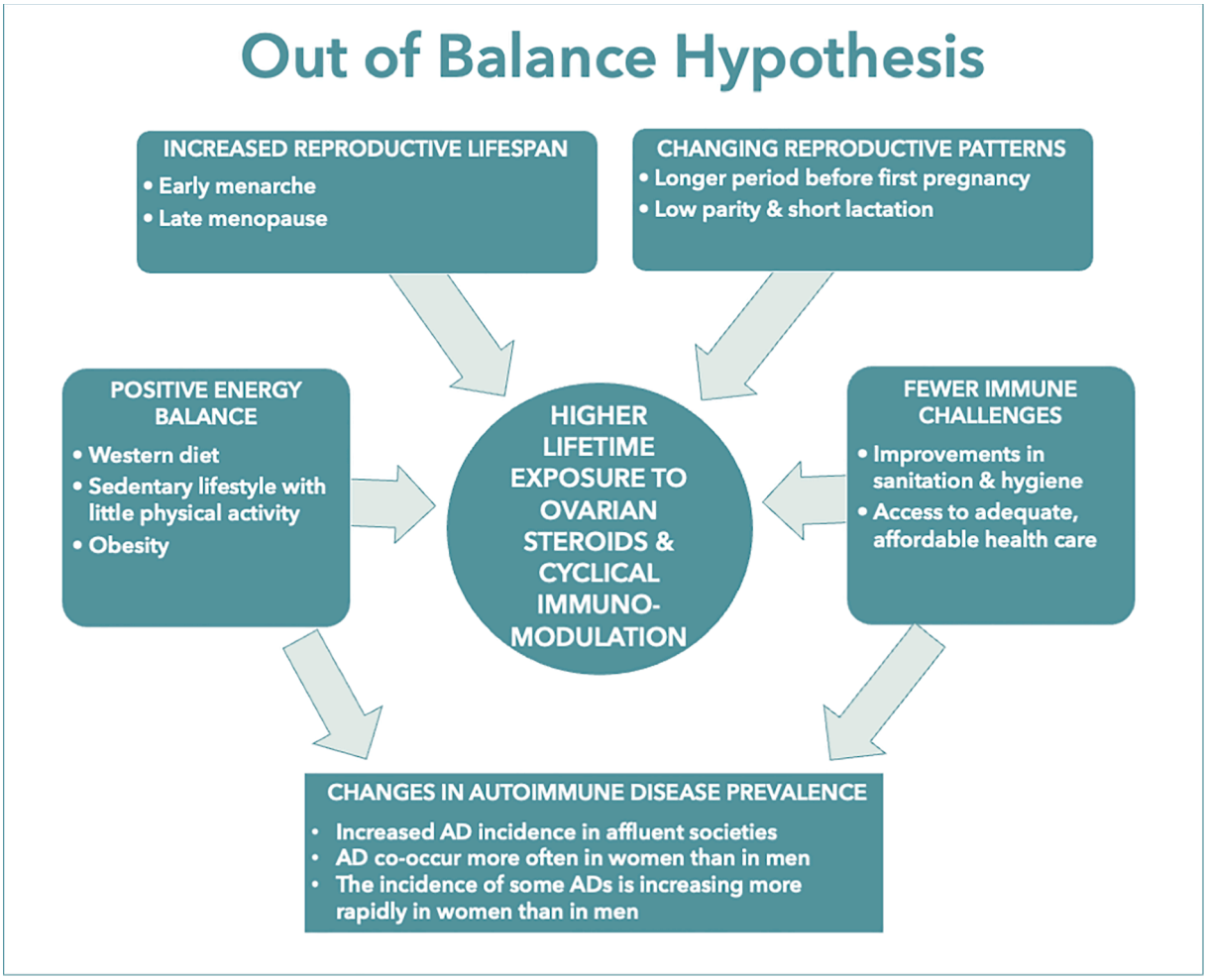

Fig. 3. The Out of Balance Hypothesis. This figure outlines various factors that can increase our lifetime exposure to ovarian steroid hormones and cyclical immunomodulation. Although originally increases in lifetime oestrogen exposure have been implicated in the development of reproductive cancers, we propose that high lifetime exposure to ovarian steroid hormones, especially oestrogen, can also have a profound impact on the immune system and subsequent autoimmune disease development. This figure uses information from the following sources: Jasienska [62], p. 15, Natri *et al.* [20] and Núñez-de la Mora and Bentley [135].

twelve may also experience higher serum oestradiol levels during their menstrual cycles [27]. Longer lifetime exposure to ovarian cyclicity and its associated hormones can impact autoimmune disease development as research has suggested that earlier age of menarche causes **multiple sclerosis (MS)** symptoms to occur earlier and be more severe [11,28,29].

Changing reproductive patterns

In comparison to the contemporary natural fertility populations as a

reference point for the female reproductive patterns for most of human evolution, women in (post-) industrialised societies spend a longer period cycling before first pregnancy, have fewer children, and spend less time breastfeeding [30]. Compared to modern-day foraging populations, the mean age of menarche in (post-)industrialised, affluent context is nearly four years earlier, and affluent women in the United States spend approximately twelve years cycling before having a first child, compared to only three years in contemporary hunter-gatherer populations [30]. Whereas women from subsistence populations breastfeed for approximately 17 years over their reproductive lifespan, the total years of lactation in American women is only 0.5 [30]. Indeed, research among Dogon women in Mali suggests that women in natural fertility populations only cycle regularly if they are infertilei, with fertile females experiencing about 100 menstrual cycles over their lifetime compared to more than 300–400 hundred in women living in (post-) industrialised, affluent contexts in the United States [31]. Women are exposed to sharp increases and decreases of regulatory lymphocytes during each menstrual cycle [32], which means that delayed pregnancy and associated **Treg** increases in combination with reduced parity could maintain the immune system in a pro-inflammatory state for longer periods of time Natri et al. [20]. As predicted then, delayed pregnancy and nulliparity are a risk factor for developing inflammatory autoimmune diseases such as **MS** [33] and **rheumatoid arthritis (RA)** [34]. Further research in diverse reproductive ecologies is needed to investigate how the number of menstrual cycles over a woman's lifetime affects overall **Treg**-pool and peripheral **tolerance**.

Fewer immune challenges

Peripheral **tolerance** can be influenced by changes in microbial exposure, which also affects reproductive ecologye and thereby ovarian steroid levels. Proponents of the hygiene hypothesis, recently renamed as the "Old Friends Hypothesis", have suggested that the transition to modern urban lifestyles depletes populations in (post-)industrialised, affluent contexts of the environmental input from co-evolved microbial organisms during early development, as a result of which their immune systems have become deregulated [35–38]. Pathogen exposure can also lead to more anovulatory cycles and oestrogen dysregulation [39], but in sanitised urban environment this occurs less frequently. Additionally a decrease in early life immune stressors may alter timing of maturation and menopause as well as ovarian hormone levels during the reproductive lifespan [40]. For example, Bangladeshi women that came to the U.K. as childrenchi have been observed to have an earlier age of menarche and higher progesterone levels than women who remained in Bangladesh [41], which Nuñez-de la Mora and collaborators have suggested to potentially be the result of fewer immune challenges during development and better sanitation and health care access in London compared to Sylhet.

Positive energy balance

Positive energy balance and increased adiposity associated with a (post-) industrialised, affluent lifestyle can also have distinct effects on the immune system, ovarian steroid levels, and reproductive lifespan. Adiposity increases the bioavailability of sex steroids in the blood [42] and enhances the local oestrogen production in adipose tissue [43]. A sedentary lifestyle with reduced physical activity is associated with higher oestradiol levels during the menstrual cycle of women of reproductive age, thereby contributing to a higher lifetime cumulative exposure of this hormone [44]. Obesity might also cause a subclinical chronic inflammatory state, exacerbating autoreactive **Th1/Th17** effects and favouring the differentiation of **Th cells** into **Th17** cells instead of **Tregs** [45,46]. Leptin, a key adipokine which is twice as high in women than in men, also promotes the **Th1** differentiation and inhibits **Treg** proliferation, thereby affecting peripheral **tolerance** [47]. Some studies have additionally found that a combination of low birth weight, early menarche, and excess weight in adulthood also leads to elevated oestradiol levels measured over a single menstrual cycle [48,49]. Although there is some research on the correlation between obesity and autoimmunity [47], no study has addressed the potential combinatory effect of obesity and hormonal changes occurring during reproductive transitions on peripheral **tolerance**. For example, it could be that the combined effects of excess adiposity and ovarian steroid exposure may contribute to increasing sex disparities in autoimmune disease incidence starting with puberty. As predicted, women that experienced childhood obesity, early menarche, and overweight in adulthood are at higher risk for developing certain inflammatory, **Th1/Th17** mediated autoimmune diseases, such as **MS** [8,29]. Understanding the combined effect of excess adiposity during menopause might especially be relevant because of the existence higher total and **unopposed oestrogen levels** during this reproductive transition [50,51] and reduced peripheral **tolerance** due to the ageing of the immune system [52].

Below we explore the current state of the evidence that underlies these predictions and may strengthen our proposition that the observed increase in autoimmune disease prevalence and changing incidence patterns might be caused by a mismatch in immune **tolerance** and cyclical **immunomodulation** mechanisms.

Proximate mechanisms by which ovarian steroids influence tolerance and cyclical immunomodulation

Various steps during the normal development and maturation of adaptive immune cells prevent the development of autoimmunity by inducing immune **tolerance** to healthy bodily tissues through deleting or neutralising **autoreactive** immune cells [53]. These mechanisms can be subdivided in **central** and **peripheral tolerance** depending on whether they take place during the early development of the adaptive immune cell in the thymus or only after they have been released into the circulation. Whereas reduced central **tolerance** may cause autoreactive lymphocytes to escape stringent selection processes during development and enter the circulation, reduced peripheral **tolerance** can cause the subsequent activation of these **autoreactive** cells. As we will describe, oestrogen and progesterone can influence both central and peripheral **tolerance**, thereby influencing autoimmune disease risk, and affecting immunomodulation, specifically balances between **T regulatory** and **Th17 cells.** In Explanatory Box 2 we offer an overview of the adaptive immune system and associated cytokines and explain the difference between **humoral** and **cellular** arm of the immune response, which is essential for understanding predictions regarding changes in patterns in autoimmune disease incidence.

Immune tolerance during reproductive transitions: the role of AIRE

During development in the thymus, T cells undergo a complex negative selection process in which T cells with too high affinity for self-antigens are deleted, whereas those with weak interactions develop into normal T cells (Fig. 5a) [54,55]. Those with an intermediate autoreactivity are positively selected to form long-lived population of native **Tregs** harbouring the ability to suppress other immune cells [53,54,56–58]. **Central tolerance** induction is enabled by the transcription of the autoimmune regulator (AIRE), which stimulates medullary thymic epithelial cells (mTECs) to express tissue-specific self-antigens (TSA) from various places around the body, allowing the training of immature T cells [53,59]. Genetic deficiencies or defects in AIRE transcription factor makes the carriers more likely to have multiple, co-occurring autoimmune diseases, and autoreactive T cells and autoantibodies [59].

Oestradiol, the main oestrogen hormone during the menstrual cycle, may influence the process of central **tolerance** induction via AIRE [54]. Due to the involvement of T-follicular-helper cells in their maturation, B cell **tolerance** is thereby affected as well [59,60]. In healthy individuals,

Explanatory Box 2
Cellular and humoral immunity and associated T-helper cells and cytokines

Autoimmune diseases can broadly be classified as originating from the **humoral** arm of the adaptive immune response, encompassing B cells and antibodies, or as being mediated by cellular immunity, comprising immune cells such as cytotoxic T cells and macrophages [71,159] (Fig. 4 & Table 1 [4,7,69,98,107,117,160–164]). This classification is based on the way that different types of **cytokines** mediate the differentiation of T-helper (Th) cells into different types which coordinate the healthy immune response [122,165]. **Cytokines** enable cross-communication and coordination between innate and adaptive immune responses [166], which is how the immune system is able to effectively eliminate unwanted intruders. Anti-inflammatory **cytokines** promote **Th2** differentiation and are responsible for activating the **humoral** immune system vital for protection against extracellular parasites [71,167]. Cellular immune responses, facilitated by **Th1** and **Th17** cells, are important for the eradication of cells infected by intracellular pathogens and viruses and are activated by pro-inflammatory **cytokines** (71,159). Finally, specialised **T regulatory cells** (**Tregs**) supervise the functions of effector Th cells by suppressing immune responses, playing a key role in autoimmunity [166,168].

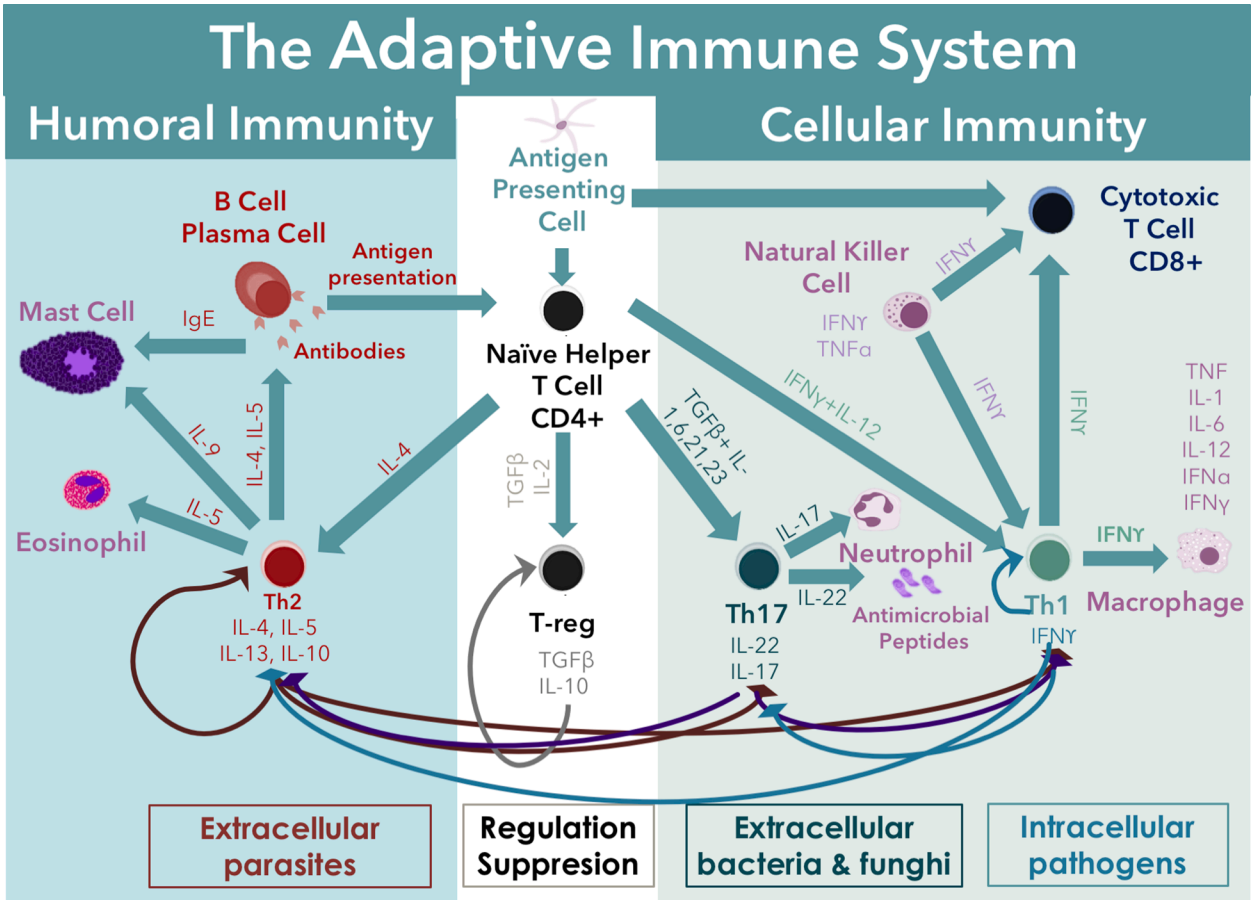

Fig. 4. An overview of the human adaptive immune system and its associated cytokines. The adaptive immune system can roughly be subdivided into humoral and cellular responses, which are mediated by Th2 or Th17 and Th1 cells respectively. Tregs supervise the activities of the different immune responses and play an important role in the regulation of the immune system. Illustration drawn based on [164,168,169, b0170 b0165,171].

Table 1
Cytokines and their effects. Immune cells secrete various cytokines with different functions, which have either stimulatory or inhibitory effects on the cellular or humoral arms of the immune system. Tregs suppress and control the different responses and are important in the maintenance of peripheral tolerance.

Cell of origin	Cytokines	Stimulate	Inhibit	Function
Th1	IFNγ	Th1, macrophages	Th2, Th17	Intracellular pathogens
Macro- phages	IL-1, IL-6, IL-12, IL-18, IFNα, IFNγ	Inflammation, fever, acute phase response, plasma cell formation		N/A
Th17	IL-22, IL17	Neutrophils, antimicrobial peptide-production	Th1, Th2	Extracellular bacteria, fungi
Treg	TGFβ, IL10	Tregs		Suppression/ Tolerance
Th2	IL-4, IL-5, IL-13	Th2, B cells	Th1, Th17	Extracellular parasites

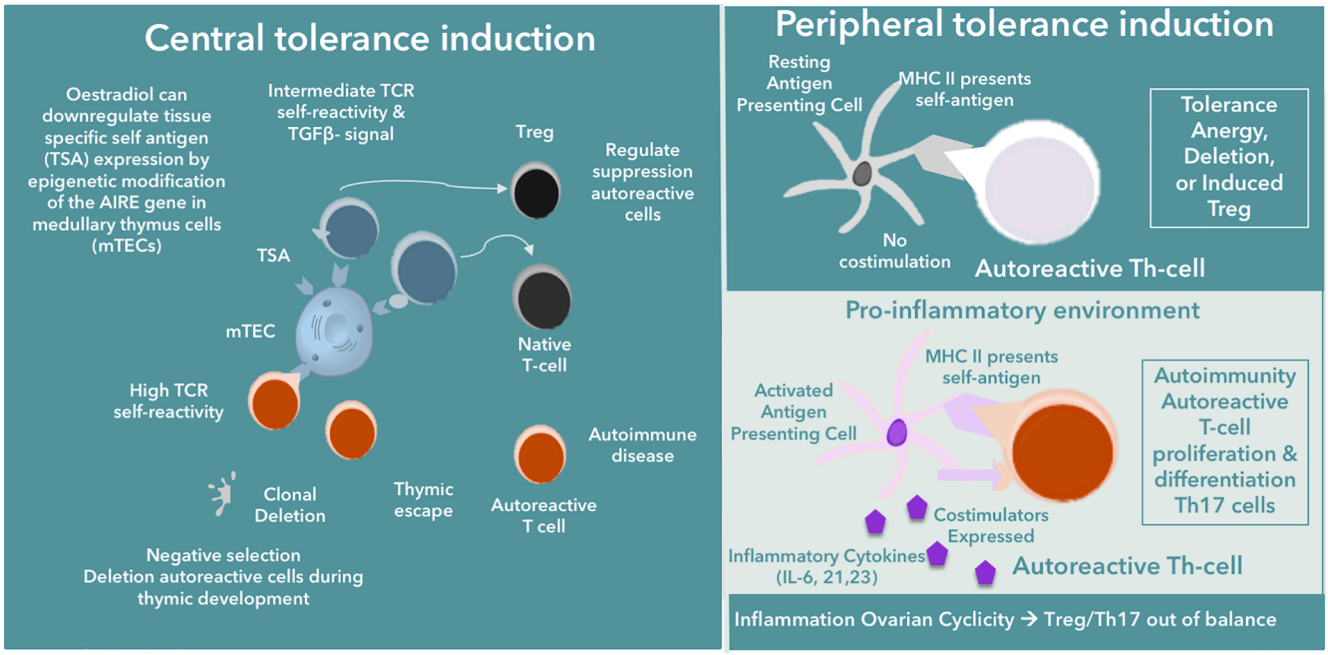

Fig. 5. Sex hormones influence central and peripheral tolerance induction. 5a (left): central tolerance induction in the thymus. Oestradiol causes the downregulation of the Autoimmune Regulator (AIRE) gene in mTECs, decreasing the expression of TSAs. This consequently decreases central tolerance induction during T cell development, and might contribute to sexual dimorphism in autoimmune disease incidence. 5b: peripheral tolerance induction. The ovarian hormone fluctuations of the menstrual cycle influence systemic inflammation levels. An inflammatory environment favours Th17 differentiation over the induction of Tregs and might therefore alter the delicate balance between Th17 and Treg cells.

AIRE expression is epigenetically down-regulated by oestradiol but up-regulated by the androgen dihydrotestosterone (DHT) [54]. As a consequence, females express less AIRE in their mTECs during the reproductive period, causing differences in central **tolerance** after the hormonal sexual dimorphism of the pubertal transition [54,61]. As AIRE is important in preventing autoimmunity, we would predict that under the influence of increases in oestradiol, women will be more likely to develop an autoimmune disease than men and to suffer from co-occurring autoimmune diseases. An increase in lifetime ovarian steroid exposure as predicted by our hypothesis might affect mechanisms of central **tolerance** induction through oestrogen-mediated down-regulation of AIRE expression in the thymus, as a result of which negative selection of autoreactive immune cells is reduced under a threshold that makes women more susceptible for autoimmunity and developing co-occurring autoimmune diseases [54,62].

Tolerance during the menstrual cycle: the role of inflammation

If autoreactive lymphocytes escape the stringent selection processes during development and start circulating around the body, specialised **Tregs** and B regulatory cells are usually still able to suppress them [54,63] (Fig. 5b). In absence of necessary co-stimulatory 'danger' molecules autoreactive lymphocytes are neutralised, and under the influence of **cytokine** TGF-β autoreactive T cells can even be induced to become **Tregs** themselves [64–66]. Yet they are less stable in their function than thymus-derived **Tregs** because of their shared differentiation pathway via TGF-β with **Th17 cells**, which play an important role in **cell-mediated** autoimmune disease (see Fig. 5). A pro-inflammatory environment favours **Th17** differentiation of these lymphocytes and can thereby alter the balance between **Tregs** and **Th17** cells [60,67].

Ovarian hormone changes may influence peripheral **tolerance** by contributing to increases in systemic inflammation, as measured using CRP-levels in the blood [68], at certain points in the menstrual cycle (Fig. 6). Oestrogen, especially oestradiol, has a dose-dependent effect on the proliferation of certain types of Th cells during the menstrual cycle, with low doses in the follicular phase favouring cellular immunity and **Th1** and **Th17** cell proliferation, whilst high levels around ovulation promote **humoral** immune responses mediated by **Th2** cells [69,70]. During the luteal phase, progesterone additionally induces **Th2 cytokine** production [71,72], away from the pro-inflammatory **cytokines** that favour **Th17** differentiation over **Tregs**. Additionally, oestradiol stimulates expansion of **Tregs** during the luteal phase, which might be important for successful implantation of an embryo during this time [32]. Thus, whereas an inflammatory environment and stronger **Th1/Th17** responses characterise the follicular phase, **Th2/Treg** levels seem to be elevated during the luteal period of the menstrual cycle. Combined with the effects of the ovarian steroids on **cytokine** production depending on menstrual cycle phase, one would expect ovarian steroid levels to affect autoimmune disease symptoms by changing the balance between **cellular** and **humoral** immune responses.

Tolerance during pregnancy: the importance of Th cell balances

Similar to the luteal phase of the menstrual cycle, pregnancy is characterised by an anti-inflammatory **Th2/Treg** immune profile. During early pregnancy, the progesterone increase stimulates the preferred differentiation of naïve T-helper cells into **humoral** immunity promoting **Th2** cells [73], whereas at the same time hCG and oestrogen induce **Treg** expansion at the implantation site and in the blood [74–77]. Research suggests that appropriate **Th1/Th2** and **Th17/Treg** balances might be important for successful gestation of a **semi-allogeneic** foetus, as the peripheral blood and decidua of women with unexplained recurrent spontaneous abortion have a reduced **Treg** proportion compared to **Th17** cells [78]. In women with preeclampsia, another disorder of pregnancy, **Treg** and **Th2** cell numbers are declined in the umbilical cord blood [79]. Elevated **Th1** and **Th17** percentages, higher inflammatory **cytokine** ratios, and decreased **Treg** percentages in early pregnancy are in contrast associated with developing preeclampsia later in pregnancy [80]. Although further research is necessary to verify whether women with a strong innate pro-inflammatory **cytokine** profile before pregnancy are more likely to develop preeclampsia later on, the optimal balance between Th cells as well as pro- and anti-inflammatory

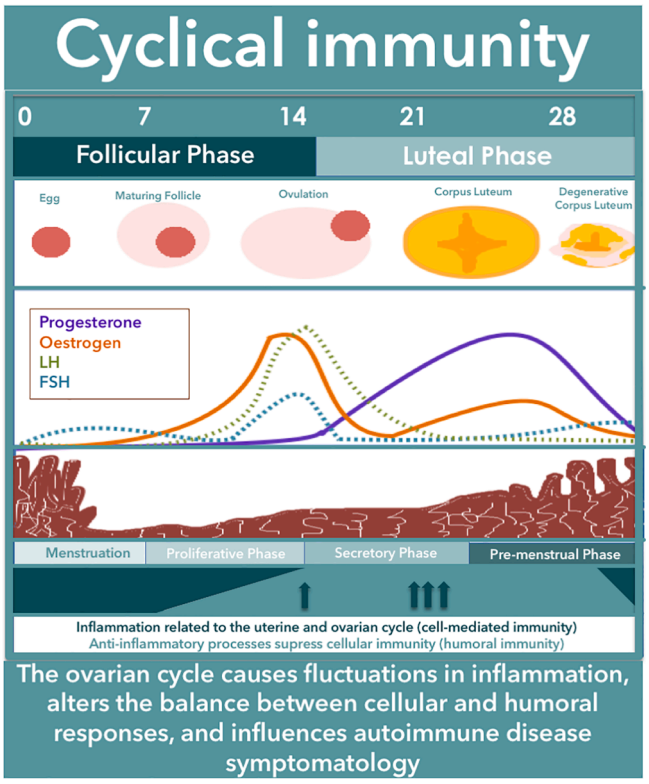

Fig. 6. Human cyclical immunity. This figure represents the ovarian cycle, which can be subdivided in the follicular and the luteal phase. It shows the developing egg, ovulation, the corpus luteum, and its degeneration, and concurrent changes in ovarian and pituitary hormone levels. The third panel depicts the uterine menstrual cycle and its phases, including the growth and decline of the uterine lining. Finally, the lower panel shows how the ovarian cycle may influence cell-mediated and humoral immunity. The arrows highlight some inflammatory occurences in the menstrual cycle during the humoral mediated phase, which are (i.) the inflammatory process at ovulation just after the egg is released and (ii.) the inflammatory processes involved in decidual differentiation at the start of the reproductive window (days 20–23). Low oestrogen levels during the follicular phase favour Th1/Th17 differentiation, whereas in the luteal phase high progesterone and oestrogen promotes Th2 responses. Consequently symptoms of cellular-mediated autoimmune diseases ameliorate during the luteal phase in most women whereas those of humoral autoimmune diseases worsen during this period. This figure was inspired by Alvergne & Tabor [85].

immune responses might be important for successful gestation. The expansion of **Tregs** suppressing cellular responses against the **semi-allogeneic** offspring, might at the same time enhance the peripheral suppression of autoreactive immune cells during gestation [81]. Combined with the shift towards a **Th2**, anti-inflammatory immune profile, this would predict that during pregnancy the symptoms of autoimmune disease patients might improve for those suffering from **cell-mediated**, inflammatory autoimmune disease such as **RA** or **MS**, whereas those with an antibody mediated, **humoral** autoimmune disease disease would experience exacerbations of their symptoms.

Reproductive hormone levels influence autoimmune disease symptoms and incidence

Hormonal changes during the menstrual cycle influence the symptoms of women with autoimmune diseases. In some women suffering from the relapsing-remitting form of **MS,** an inflammatory, **cell-mediated** autoimmune disease of the nervous system, symptoms ameliorate during the luteal phase in which cellular immunity is more suppressed, but worsen again during the premenstrual decline in sex hormone levels [82–84]. This cyclical effect seems however to be limited to a subgroup **MS** patients [83,84]. On the opposite side of the autoimmune disease spectrum, the surge in anti-inflammatory **cytokines** and the stimulation of the **Th2** cells during the luteal phase affect patients suffering from **humoral** autoimmune disease differently [69,85]. Women with **systemic lupus erythematosus** (**SLE**), a **humoral** autoimmune disease caused by autoantibody production towards various organ systems, experience an exacerbation during the luteal phase of the menstrual cycle when **Th2** responses dominate, with 80% of symptomatic flares occurring during this period [86]. The complex dynamics by which reproductive hormone changes associated with the menstrual cycle influence the symptoms of autoimmune diseases warrant further investigation, also to understand why these effects occur only in a subset of patients.

As predicted based on this review of the role of ovarian steroids on **immunomodulation**, the increase in anti-inflammatory **cytokines** and a **Th2/Treg** immune profile during gestation pregnancy has an ameliorating effect on the symptoms of **RA**, a **cell-mediated** autoimmune disease. Marked disease remission in up to 75% of pregnant patients with active **RA**, often to such an extent that medication can be drastically reduced [17,87,88]. This was already reported in the scientific literature as early as 1938 [88]. However, postpartum, when oestrogen and progesterone concentrations fall, 90% of these patients experience a revival in disease activity concurrent with a shift back to a stronger cellular response [70,89,90]. In contrast, women with **Graves autoimmune thyroiditis**, a **humoral** autoimmune disease mediated by TSH-receptor auto-antibodies [91,92], experience a worsening of their disease early in pregnancy, but have their symptoms improve again later on, probably due to the positive effects associated with **Treg** increases [93,94].

Acknowledging the importance of these observations, biomedical research has long focused on finding potential treatments for alleviating the symptoms of autoimmune diseases using exogenous hormone administration, especially testing the benefits of oestradiolin mouse models of **MS**. For this disorder, oestradiol administration has been shown to decrease disease severity and even delay disease-onset [95,96]. Similarly, a case-control study in humans found **MS** incidence to be 40% lower in women who took hormonal contraception in the last three years, suggesting that high exogenous oestrogen levels may even delay the incidence of the first clinical attack of this **cell-mediated** inflammatory autoimmune disease [95,97]. However, on the other end of the spectrum, studies suggest that exogenous hormone administration might increase the incidence of developing **humoral** autoimmune disease such as **SLE**, with combined oral contraceptive starters being at a heightened risk [98,99]. The risk of developing **SLE** increases with greater concentrations of ethinyloestradiol in the pill formulation and is higher in women using first- or second-generation contraceptives that are known to have higher oestrogen doses compared to more modern drug formulations [99,100]. As predicted by our hypothesis, postmenopausal exogenous oestrogen use also increases women's **SLE** risk, and randomized, double-blind controlled trial of hormone replacement therapy in **SLE** patients slightly increases the risk of mild to moderate flares [101–103]. Oestrogen levels therefore influence not only symptoms of autoimmune disease, but might also be a contributing factor to autoimmune disease incidence, possibly by affecting central and peripheral **tolerance** induction mechanisms.

Changes in endogenous sex hormone levels during the reproductive transition of puberty may also increase the incidence of autoimmune disease in women, shifting the sex ratio towards female preponderance. A Finnish cohort study found that girls during childhood are not more likely to present with **type 1 diabetes T1D** than boys overall [104], yet at age thirteen 87.5% of newly diagnosed **T1D** patients in the same cohort was female, coinciding with the age of menarche in the country [105]. Generally considered to be a childhood onset disease, T1D actually peaks at several points during the lifespan - during childhood (ages of 5–7), around puberty, and in the fifth decade around menopause

- suggesting a role for shifting sex hormone levels during reproductive transitions in triggering autoimmunity [106,107]. Even in autoimmune diseases that are predominantly female, changing oestrogen levels associated with reproductive transitions may widen the incidence gap between women and men. For example, before puberty **SLE** already affects 3–4 girls for every boy, but during the childbearing years the incidence gap increases to as much as 9–20 females for every male [85,108,109]. A Chinese study furthermore found that although during the reproductive period **SLE** incidence was 13.3(f):1(m), the sex disparity in late onset, post-menopausal **SLE** was only 3.2(f):1(m) [110], which is remarkably similar to pre-pubertal numbers. Similarly, the sex ratio of **RA**, a **cell-mediated** autoimmune disease characterised by chronic inflammation of bone and cartilage [69], is 6(f):1(m) during the childbearing years but approaches 1(f):1(m) again for older ages of onset [111,112]. These epidemiological studies suggest that concurrently with the sexual dimorphism of reproductive hormone levels during the childbearing years, a change in autoimmune disease incidence takes place, and that changes in endogenous levels of ovarian steroids might affect autoimmune disease incidence.

Evolutionary perspectives on the sex disparity in autoimmune disease

What can an evolutionary perspective bring to research on the influence of sex hormones on autoimmune disease incidence and symptoms? An evolutionary perspective acknowledges that our bodies are "*bundles of compromises*" shaped by natural selection with the ultimate purpose of reproducing and passing down our genes to subsequent generations [62,113,114]. Natural selection consequently preferentially acts on traits conferring an adaptive advantage before or during the childbearing years. As a consequence traits that are detrimental to health in post-reproductive life, including those contributing to increased autoimmunity, will still be inherited if they confer an advantage during reproduction or early survival [62,115–119]. Therefore, the regulatory effect of ovarian steroids on central and peripheral **tolerance** induction in women might have evolved to ensure immune non-reactivity to paternal antigens displayed by the placenta during pregnancy to optimise reproductive success [20], yet these interactions might become deregulated in post-reproductive life. Accordingly, the evolution of placentation in mammals may have led to sex-specific selection on immune function to induce tolerance to semi-allogeneic foetal antigens while still combating pathogens in pregnant mothers [20]. This could have left women at increased risk for autoimmune disease compared to men. Similarly, it has been suggested that a strong inflammatory response may be beneficial to survival in early life, whereas it might be detrimental to health in old age when **Treg** populations have declined, and chronic inflammation is associated with incidence of **Th1/Th17** mediated autoimmune diseases such as **RA** [120,121].

Secondly, **life history theory**, a branch of evolutionary biology, predicts that organisms optimise fitness in interaction with environmental conditions through energy trade-offs between growth, reproduction, and somatic maintenance, including immunity, both over their own lifespan and across generations [85,122]. The observed variation in immune profile in women during the reproductive period suggests the existence of such a trade-off between reproduction and somatic maintenance. Following the importance of an anti-inflammatory **Th2/Treg** response during pregnancy, it has been previously hypothesised that women with innate **cytokine** profiles promoting **Th2/Treg** responses have a selectional advantage based on their enhanced ability to conceive [123,124], whereas women with elevated **Th1** cell levels compared to **Th2** responses are more likely to be subfertile [123,124] and at higher risk of implantation failure during IVF-treatment [125]. This is because women with strong **Treg** responses have a more tolerant response to the implantation of a **semi-allogeneic** embryo [126], and by increasing antibody production during pregnancy, the mother can provide her offspring with short-term passive immunity whilst the foetus' own adaptive immune system develops [127]. This shift to **humoral** responses during pregnancy preferentially enhances the production of IgG-antibodies, which is a type of antibody unique to mammals [128] and the only maternal immune factors capable of crossing the placental barrier to the offspring [127]. However women with such a **Th2/Treg** profile might however be more susceptible to certain pathogens because of the inhibitory effect of anti-inflammatory **cytokines** on **Th1** responses, suggesting a trade-off between reproduction and survival [123,124].

Thirdly, considering the importance of immune profile for maternal tolerance as well as pathogen defence and subsequent autoimmune disease risk, more research is needed on autoimmune disease incidence in different (pathogen) ecologies to understand the wide-reaching consequences of these trade-offs between immunity and reproduction. Although research on immune function under different subsistence ecologies is limited, studies looking at Tsimane horticulturalists in Bolivia revealed that the infection with some helminths, such as roundworm which elicit a Th2 immune response, decreases age of first birth [129]. Yet, infection with some other parasites and receiving anthelminthic medications are associated with a lower chance of conceiving [129]. Because of a complex pathogen environment, Tsimane experience elevated immunological parameters associated with inflammation compared to (post-) industrialised, affluent populations [130], but not higher autoimmune disease incidence [131]. This is possibly because the higher rate of helminthic infections induce **Th2/Treg** responses, that regulate excessive inflammation [130]. As a first study of its kind, Hové *et al.* (2020) additionally investigated differences in changes in immune function between Tsimane and American women during pregnancy [132]. Tsimane females were found comparatively have higher lymphocyte (**Th1**) as well as eosinophil (**Th2**) counts than pregnant women in the United States, but experience lower levels of inflammation in later pregnancy. The authors suggest that continuous exposure to pathogens , which can also cause miscarriages, may influence the dynamicity of immunomodulation and tolerance during pregnancy in the Tsimane ecology. Investigating the complexity of pathogen ecology in relation to **immunomodulation** is necessary to enhance our understanding of interactions between women's immune profiles and fertility, as these trade-offs may in turn affect autoimmune disease risk.

Finally, an evolutionary medicine perspective highlights the importance of investigating the effect of recent changes in the ecology under which the interactions between the reproductive and immune system originally evolved, which can be considered a 'mismatch'. Using the concept of **WEIRD** (Western, Industrialised, Rich, and Democratic) taken from the field of psychology [21], evolutionary anthropologists have argued that conventional biomedical research currently too heavily relies on participants of European descent living in urban, industrialised contexts, which are not representative of the lifestyle and ecological pressures experienced by our ancestors [133]. Most biomedical research on autoimmune diseases and sex hormones originates from (post-) industrialised, affluent societies that have adopted a Western lifestyle, which is not reflective of the energetic conditions during most of human evolution. Current immunological studies consequently fail to appreciate the existence of substantial variations in reproductive hormone levels between populations, members of the same group, and even between different cycles of the same woman [134]. Gene polymorphisms only partially account for these differences, which are instead the result of variations in age, ecology, and energetic factors that affect metabolic energy availability and their reallocation to vital functions other than reproduction [62,135]. Hormones are key modulators in the optimal investment of energy into these competing physiological functions and influence the timing of life-history events, such as the pubertal transition and menopause [136,137]. They are the mechanism by which organisms adapt cellular functions across different tissues in response to endogenous and exogenous environmental factors [138]. Therefore, gonadal function is sensitive to ecological influences, such as immune challenges, nutrition, and energy expenditure

[139,140]. Additionally, conditions during early development create set points for the regulation of the reproductive axis in adulthood leading to differences between populations as well [62,139,141]. It is for these reasons that ecological changes which are able to alter endogenous hormone levels, thereby potentially increasing the risk of autoimmune disease,deserve much more attention in biomedical research.

What about testosterone and men?

In this paper we have mainly focused on the effect of the 'female' sex hormones on the adaptive immune system, neglecting the role of the testosterone in central and peripheral **tolerance** induction and **immunomodulation**. Similarly to women, men who transition towards a Westernised, (post-) industrialised, affluent lifestyle also experience higher sex steroid levels. For example, Bangladeshi men who migrated to London, UK, in early childhood experience higher testosterone levels than their counterparts that remained in the rural parts of Bangladesh [144]. Thus we predict that whilst increases in oestrogen and progesterone may put women at an increased risk of developing autoimmune diseases, an opposite trend may be taking place in regard to men and testosterone. Although discussing the full implications of this research is beyond the scope of this paper, the influence of changing testosterone levels following the adoption of a modern Westernised, (post-)industrialised, affluent lifestyle should also be investigated in the context of autoimmune disease in men.

Although androgens such as testosterone promote **cytotoxic T cell** proliferation, compared to women men display lower **humoral** and **cellular immune** activity, which are the arms of the adaptive immune system involved in the development of autoimmunity [11,54,145,146]. **AIRE** expression, which is implicated in central tolerance, is epigenetically up-regulated by the androgen dihydrotestosterone, as a consequence of which males express more AIRE in their mTECs than females during the reproductive period [25,55]. This may cause a difference in central **tolerance** after the hormonal sexual dimorphism occurs. Additionally, testosterone may play an important role in autoimmune disease progression and symptoms. In a study of **MS** patients, women with the lowest testosterone levels as well as men with the highest oestradiol levels experienced more brain lesions [89]. Furthermore, in obese men there is an even more distinct increase in plasma oestrogen levels compared to women [147], altering relative testosterone to oestrogen ratio's due to excess adiposity. In this context, there is a dearth of studies focussing on the importance of relative hormone ratio's rather than absolute hormone levels on autoimmune disease risk, whereas for cardiovascular diseases research seems to suggest that determining relative testosterone to oestrogen ratio's may be a more valuable predictor than looking at either hormone in isolation [148]. Finally, despite an abundance of studies suggesting that hormonal changes over the life span affect autoimmune disease risk in women, no such research has been conducted in men, despite a documented age-related drop in the production of testosterone and other androgens during **andropause,** whilst oestrogen levels remain similar [149,150].

Conclusion and future directions

Of all immunology articles, less than 10% considers the sex of the participants in their analysis [151] and this bias persists in animal model studies [152]. Although compared to other areas of biomedicine autoimmune disease research has already acknowledged that taking sex and parity into consideration is key to understanding the female preponderance in autoimmunity incidence, research on the proximate mechanisms by which reproductive hormones influence **tolerance** mechanisms and autoimmune disease symptoms would benefit from an evolutionary medicine framework. A key part of this approach is recognising the diversity in sex hormone levels and immunomodulation in response to ecological pressures, and the effect these interactions might have on the immune system of women according to their reproductive life stage and energy balance [122,153].

To fully understand how this diversity in sex hormone profiles can contribute to differences in autoimmune disease incidence, there is also a need for more immunological research to take place outside of (post-) industrialised, affluent settings that are more reflective of the energetic conditions and challenges encountered in our ancestral environment [133]. This is necessary to understand how novel changes in energy balance and lifestyle might affect autoimmune disease development. For example, considering that throughout most of our evolutionary history women engaged in prolonged periods of breastfeeding [30], there is a severe lack of studies that consider the effect of lactation on the mother's immune profile and consequent autoimmune disease risk. In Tsimane women, lactational amenorrhea lasts 12–14 months, and after just 7–9 months of regular cycling women may get pregnant again [132]. Preliminary studies suggest that during lactation Tsimane women have an immune profile that is quite distinct from both normal cycling and pregnant women [154]. Yet, it is not properly known how breastfeeding duration influences tolerance mechanisms in women and subsequent autoimmune disease risk.

Although methodologically challenging, future research on autoimmune diseases should particularly focus on understanding possible variation in epigenetic regulation of the AIRE gene in response to ecological pressures and differences in oestradiol levels. Additionally, the effect of pregnancy on mechanisms of central **tolerance** deserves further attention. Research is also needed on the variation in cyclical immunity in relation to autoimmune disease incidence and symptomatology, specifically looking at fluctuations in **Treg**/**Th17** and inflammatory **cytokine** ratios across the menstrual cycle in different ecological settings, and the influence in lifetime menstrual cycles on **Treg**-pool and peripheral **tolerance**. For this purpose, it is crucial that a more flexible, context dependent approach to immunological research is created based on life history theory and evolutionary principles. This is needed to enhance our understanding of how variations in ovarian hormone levels during different reproductive stages contribute to population level differences in autoimmune disease incidence. Currently no accounts of autoimmune disease exists in subsistence populations, although this cannot be taken as prove of absence of incidence of these diseases outside of (post-)industrialised, affluent contexts, as it is highly likely that under-diagnosis and under-reporting of autoimmune disease symptoms are responsible for the absence of such accounts. Due to their low life expectancy at birth, which is skewed because of infant mortality, it is a common misconception to assume that individuals from subsistence populations may not live long enough to experience chronic diseases associated with ageing [142], such as autoimmune disorders. However, the modal age of death of adults in hunter-gathers is 68–78 years [142–143] and there are many autoimmune diseases whose onset is most frequent at earlier stages of life [10]. Immunological research will benefit from considering the reasons for differences in autoimmune disease incidence in ecologically diverse populations, taking into account evolutionary explanations for variation in sex hormones, immunomodulation, and tolerance mechanisms. As reproductive function affects the body beyond fertility and pregnancy alone, understanding interactions between sex hormones and immune system throughout women's reproductive history is indispensable for advancing female health.

Glossary

Andropause	The male equivalent of menopause, characterised by a significant drop in androgen production whereas oestrogen levels remain more stable.
Cellular immunity	is activated by pro-inflammatory cytokines and regulated by Th1 and Th17 cells. The cellular immune response offers protection against intracellular pathogens such as viruses, as well as fungi and extracellular bacteria.

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Cytokines	regulatory proteins of the immune system.
Graves disease	humoral autoimmune disease of the thyroid which involves antibodies against the thyroid stimulating hormone (TSH) receptors causing hyperthyroidism. Th2 cell mediated autoimmune disease.
Humoral immunity	consists of B-cells and their antibodies and is activatedby anti-inflammatory cytokines that cause Th2 cell differentiation. The main purpose of humoral immunity is to fight of extracellular parasites.
Immunomodulation	the modification of the responses or functioning of the immune system, either by activating or by supressing certain features of the immune response.
Life history theory	Life-history theory is a framework in biology that explains this phenotypic plasticity by predicting that, in face of constraints on the amount of resources available throughout an organism's lifespan, compromises in energetic investment into vital physiological functions are inevitable. Consequently, organisms optimise fitness by interacting with environmental conditions through trade-offs between growth, reproduction, and somatic maintenance, including immunity.
Mismatch	an evolutionary mismatch perspective suggests that our environment is changing more rapidly than we can adapt to and that there is a dyscongruence between the rate at which our bodies evolve and our rapidly changing environments and lifestyles.
Multiple sclerosis (MS)	chronic, inflammatory autoimmune disease affecting myelin in the central nervous system. This is a Th1/Th17 cell mediated autoimmune disease.
Nulliparity	A medical term for describing a woman who has never carried a pregnancy or given birth to a child.
Proximate mechanisms	according to Tinbergen's four questions in biology (1963) proximate mechanisms what the immediate cause is for a certain biological phenomenon. By asking 'how' questions immunological research helps us understand immediate causes of pathology but might neglect bigger questions, such as why vulnerabilities to certain pathologies arose to start with. These latter type of question is the domain of 'ultimate explanations'.
Rheumatoid arthritis (RA)	chronic, inflammatory autoimmune disease, which is relapsing but progressive and mainly affects the bones and cartilage. Th1/Th17 cell mediated autoimmune disease.
Semi-allogeneic	sharing some but not all genes with the mother since foetus inherits half of its genes from the father.
Systemic lupus erythematosus (SLE)	humoral autoimmune disease involving B cell hyperactivity and autoantibody production against nuclear antigens. This causes an inflammatory rheumatic disease involving multiple organ systems. Th2 cell mediated autoimmune disease.
Th1 cells	T-helper cells type 1 are important in the cellular immune response. The inflammatory cytokines they secrete stimulate macrophages but most importantly also cytotoxic-T-cells. Thus Th-1 cells are important in regulating responses to intracellular pathogens. However Th1 cells also play a role in cellular-mediated autoimmune diseases such as MS.
Th17 cells	T-helper cells type 17 are part of the cellular immune response. They secrete inflammatory cytokines and are important in the response to extracellular bacteria and fungi. They play a pathogenic role in inflammatory, cellular-mediated immune responses such as MS.
Th2 cells	T-helper cells type 2 are important in the humoral immune response. Th2 cells secrete anti-inflammatory cytokines which regulate the humoral immune response.Autoreactive Th2 cells are pathogenic in Th2 type autoimmune diseases such as SLE.
Tolerance	also known as immunotolerance, this is a state of unresponsiveness of the immune system to antigens derived of the own tissues that may have the capacity to elicit an adaptive immune response.
Tregs	T-regulatory cells' main function is the suppression and regulation of immune responses as well as tolerance. They also play an important role during pregnancy in the tolerance to a semi-allogeneic foetus. There are two types of Tregs, those that are centrally induced and those that originate in the periphery.
Type 1 diabetes	autoimmune disease causing the progressive loss of insulin-secreting cells pancreatic islets. Cellular autoimmune diseases with an occasional humoral component, especially in children.
Ultimate explanations	according to Tinbergen's four questions in biology (1963), ultimate explanations ask for the function and phylogeny of a trait or complex biological phenomenon. Ultimate explanations are guiding evolutionary anthropology/biology research and ask 'what for' rather than 'how'. For example, one may ask "how did natural selection leave our body vulnerable to developing autoimmune disease?
Unopposed oestrogen levels	during the menopausal transition, progesterone levels decline nearly a decade before oestradiol levels rapidly fall six months before menopause (age 49-51).
WEIRD	the acronym for Westernised, Educated Industrialised, Rich, and Democratic was introduced by Henrich and colleagues in 2010 to describe the unusual psychological characteristics of people living in such societies. The term is now increasingly also applied to describe the abnormal physiological features people living in these societies exhibit.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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