The role of testosterone and other hormonal factors in the development of rheumatoid arthritis

Sex-specific incidence patterns and differences in the disease phenotype between men and women suggest that hormone-related factors are important in the pathogenesis of rheumatoid arthritis (RA). Sex hormones have immunomodulatory properties that may be important in this context. Early menopause has been shown to be a predictor of RA, independent of factors such as smoking, and long-term breast feeding may reduce the risk of RA. Recently, a prospective study reported a negative association between testosterone levels and the risk of rheumatoid factor-negative RA in men. This is compatible with data indicating important anti-inflammatory effects from testosterone. These findings may improve our understanding of the RA disease process, and possibly also lead to new therapeutic strategies, including hormone substitution.

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Learning objectives

Upon completion of this activity, participants should be able to:

• Analyze the epidemiology and clinical consequences of rheumatoid arthritis (RA) among men and women

• Evaluate the relationship between sex hormones and RA among men

• Assess how hormonal treatments can affect the incidence and severity of RA

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This review spans different aspects of hormonal factors in rheumatoid arthritis (RA). It includes epidemiologic and clinical observations, a review of data on related pathomechanisms, and findings on the role of gonadal steroids in the development and the treatment of RA. It is based on a thorough study of this field over a number of years, and updated literature searches to identify recently published relevant articles through to June 2013. All articles included in the review were systematically reviewed by one of the authors. In order to assure quality, key articles were reviewed by both authors, and the assessment was based on consensus.

Epidemiology of RA: sex-specific aspects

Overall, women have a more than twofold higher incidence of RA than men. This is mainly due to an increased risk for women during their reproductive years, when the incidence shows a female:male ratio of 4–6:1 [1–3]. The peak incidence of RA in women occurs after the menopausal age [1–3]. RA is rare in men aged less than 45 years of age, but the incidence rises steeply with age [1–3]. FIGURE 1 illustrates the sex-specific incidence of RA by age group in Norfolk (UK) estimated from a population-based inception cohort of patients with inflammatory polyarthritis recruited in 1990 [3]. The case definition of RA was based on cumulative fulfillment of the 1987 ACR criteria for RA over 5 years of follow-up [4]. The incidence rates were similar when the 2010 ACR/European League Against Rheumatism (EULAR) criteria were applied at baseline [5]. In this population, the highest incidence rates in women were seen among those aged 45–74 years, whereas the incidence in men peaked later, at age >65 years, and men had a higher estimated incidence of RA than women in the 75–84-year age group (FIGURE 1). Similar age-related patterns

were reported from a retrospective survey of incident cases of RA in Olmsted County (MN, USA) in 1995–2007, although, in this population, the estimated incidence remained higher in women than in men in all age groups, including those aged ≥75 years [2].

These patterns likely represent sex-specific exposures, such as hormone-related factors. In women, major hormonal changes are associated with menopause, which is influenced by health status and lifestyle factors. In men, an average drop of 1–2% in serum testosterone levels per year after the age of 30 years has been reported, although with major variability [6]. The prevalence of late-onset hypogonadism in men increases sharply after 60 years of age [7]. This coincides with the observed increase in the male incidence of RA (FIGURE 1). However, longitudinal changes in testosterone levels in middle-aged and elderly men have been shown not to be purely age-related, but largely explained by lifestyle factors and comorbidities [8]. Taken together, this suggests complex relations between hormones, other environmental factors and RA development in both sexes. Prospective data, with exposures measured before the onset of RA, are crucial for understanding the role of hormone-related factors in disease development and expression.

Sex differences in the phenotype of RA

Sex differences for various aspects of disease severity have been described in several studies. One retrospective review of a community-based sample revealed a higher proportion with erosive disease in male patients, but a greater number of orthopedic procedures in women [9]. Furthermore, a higher incidence of vasculitis and other severe extra-articular manifestations in men compared with women has been
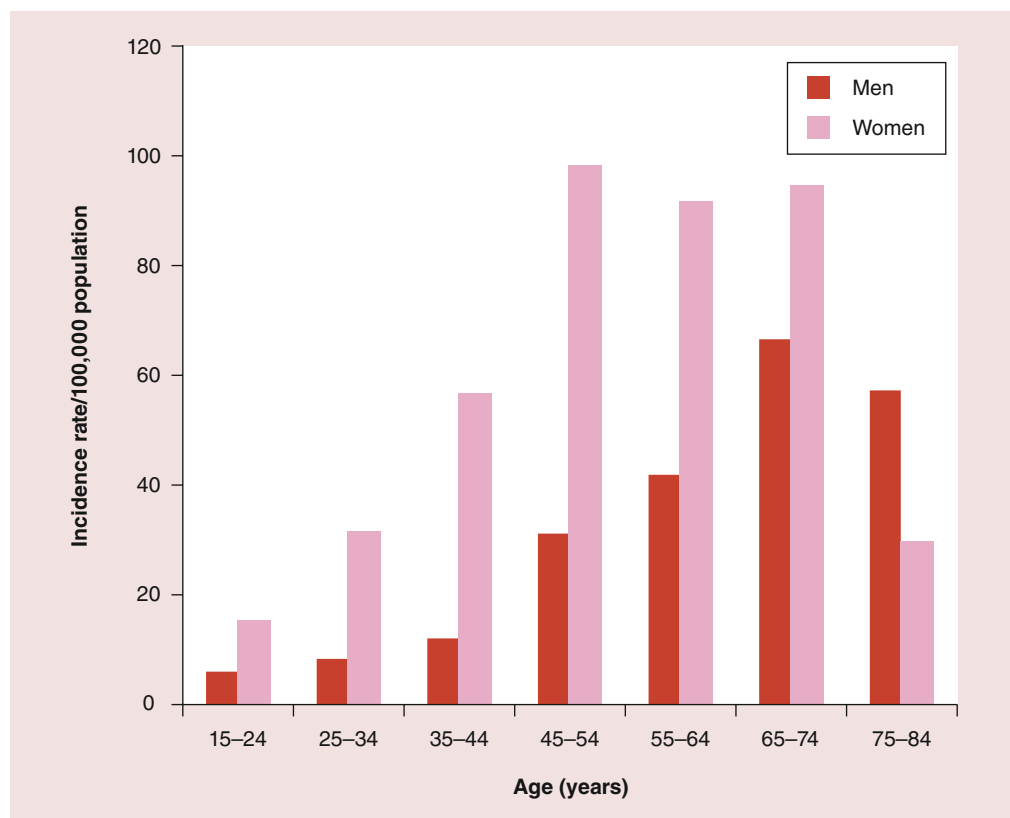
Figure 1. Incidence rates of rheumatoid arthritis per 100,000 population, by sex and age group, in Norfolk UK: from a population-based inception cohort of patients with inflammatory polyarthritis assembled in 1990. Incident rheumatoid arthritis was defined as cumulative fulfillment of the 1987 ACR criteria for rheumatoid arthritis within 5 years of follow-up. Data taken from [3].

reported [10]. In studies of a Swedish multicenter inception cohort of early RA patients, women had slightly higher disease activity, measured using the Disease Activity Score based on 28 joints (DAS28), compared with men at baseline [11,12], mainly owing to higher numbers of tender joints and worse rating of general health [12]. The difference in DAS28 between men and women increased over time [12]. However, male patients had higher C reactive protein at baseline [11]; there was no difference in baseline radiographic joint damage or progression of joint damage over time [12], although other studies have suggested that female gender may be an independent predictor of radiographic progression [13]. In the BeST study, a randomized controlled trial of four response-driven treatment strategies performed in The Netherlands, female patients were significantly less likely to achieve drug-free remission [14]. Finally, in the large multinational QUEST-RA study, women consistently had worse patient-reported outcomes than men [15]. These patterns may partly reflect factors that are not specific for RA since there is an association between chronic widespread pain

and female sex in the general population [16]. On the other hand, hormone-related factors and sex differences in relevant exposures (e.g., smoking) may also modify the disease phenotype in RA.

Immunoregulatory role of gonadal steroids

The gonadal steroids consist of estrogen, androgens and progesterone. Estrogen is mainly produced by the granulosa cells of the ovary, but also, to some degree, by the adrenal cortex, adipose tissue and testicles. There are two types of estrogen receptors (ERs), α and β. After binding, the complex translocates to the nucleus and activate estrogen response elements in gene promoters [17].

Estrogen levels vary in premenopausal women depending on their menstrual cycle, are markedly increased during pregnancy and drop significantly in the postmenopausal state. Estrogen has an important role in the maturation of the reproductive system, plays a part in the preservation of the skeleton and influences the immune system.

Estrogen can have opposite effect on immune system at high versus low levels, and distinct

effects on different cell types [18]. A stimulatory effect on B cells and both a inhibitory and stimulatory effect on T cells have been observed [19]. At physiological concentrations and in the presence of cortisol, 17-β estradiol and a combination of downstream hydroxylated estrogens may stabilize or increase immune stimuli-induced TNF secretion from human leukocytes [20]. Estrogen has been shown to stimulate IFN-γ production from T cells, but inhibit IFN-γ production from macrophages and dendritic cells [21]. Studies of murine models of RA have shown amelioration of disease during pregnancy [22]; blocking of ER-α and -β has been noted to enhance the disease [23]. A recent study of a postmenopausal murine model indicated that the therapeutic effect of estrogen was conducted via ER-α signaling pathways, and not through ER-β [24].

The main role of progesterone is to maintain pregnancy. It has been reported to downregulate the production of the proinflammatory cytokine IL-8 in rabbits [25].

Testosterone is the principal androgen, secreted mainly from the testis, but also from the adrenal cortex and the ovaries in women. In general, androgens tend to suppress humoral and cell-mediated immune responses [26], and possibly stimulate lymphocytes to a Th2 shift [27]. Mouse models of the human demyelinating disease multiple sclerosis, which is a Th1 driven autoimmune disease such as RA, showed a protective effect of testosterone via a shift from Th1 to Th2 helper response [28]. In line with this, testosterone has been shown to inhibit secretion of cytokines, such as TNF and IFN-γ, from stimulated human peripheral blood leukocytes [20]. Finally, in a recent study of young men, low testosterone levels were found to be associated with low-grade systemic inflammation, measured as increased levels of circulating TNF and other cytokines [29].

The relation between different hormones in the hypothalamus–pituitary–gonadal (HPG) gaxis and the immune system, with complex effects of estrogen and mainly anti-inflammatory effects of testosterone are illustrated in FIGURE 2.
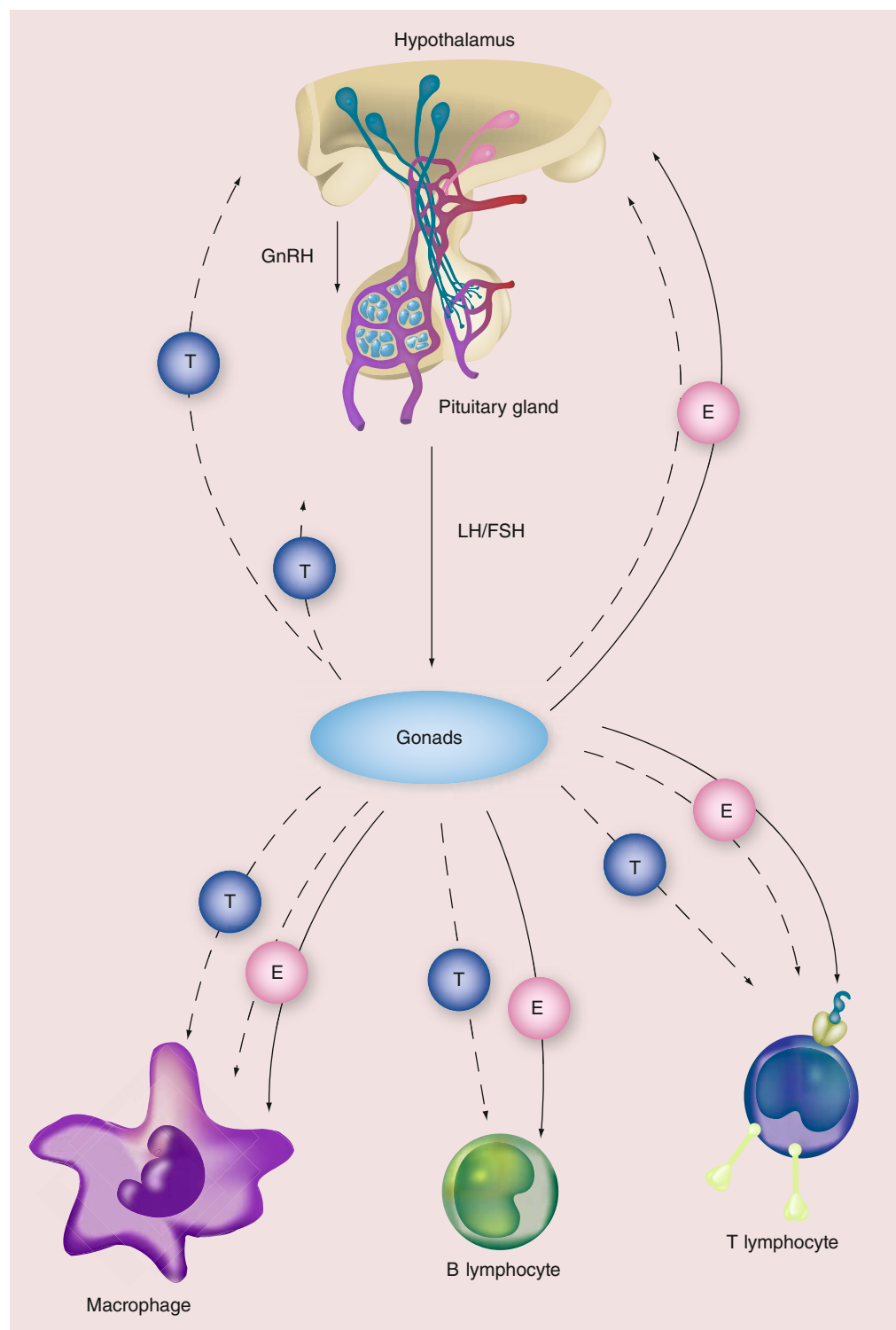
Effects of gonadal steroids in RA

Since estrogen has differential effects on the immune system, its effects on various autoimmune disorders are expected to be diverse. For example, estrogen substitution has been seen to induce flares and increase antibody production in patients with systemic lupus erythematosus [30]; however, it may have an ameliorating effect on RA patients [19].

A Swedish 2-year prospective, randomized controlled trial analyzed the effect of hormone replacement therapy (HRT) in RA, and reported significant improvement, with a decrease in disease activity, as well as in laboratory parameters, and improved bone mineral density, in the group receiving HRT [31]. A French observational study found that HRT may reduce the risk of developing RA by protecting against production of anticitrullinated peptide antibodies [32]. However, the results from the Women's Health Initiative randomized controlled trials did not confirm a positive effect on RA severity [33]. A shorter more recent clinical trial of 12 weeks, examining the effect of a selective ER-β agonist, ER-β-041, did not demonstrate any significant clinical effect on disease activity in patients with RA [34].

In the end, the benefits of HRT need to be weighed against the risks in individualized clinical decision-making. When considering HRT for patients with RA, the known increased risk of cardiovascular complications with treatment, also needs to be taken into account [35], in particular, since these patients have an elevated baseline risk related to RA [36].

Tengstrand et al. found that men with early RA had on average lower bioavailable testosterone levels [37]. Low levels of testosterone in both female and male RA patients compared with controls have been demonstrated in other cross-sectional studies [38,39]. Furthermore, low levels of testosterone have been observed in synovial fluids in both female and male patients with active disease [40]. Since chronic inflammation is known to lower testosterone through conversion to estrogen, it is difficult to determine if the low androgen levels are due to effects of inflammation or vice versa [41]. Treatment with testosterone has been reported to have a positive, but modest, disease modifying effect among postmenopausal women with RA [42]. Only small trials of testosterone substitution have been performed in male patients with RA, with conflicting results [43,44].

A role for testosterone in limiting arthritis is supported by recent studies of the SKG mouse arthritis model [45]. In this model, arthritis prevalence and severity was greater in female mice, but absence of testosterone in male mice after orchiectomy led to increased arthritis, as well as more extensive interstitial lung involvement [45]. Furthermore, higher levels of anti-citrullinated peptide antibodies (ACPA) were detected in orchiectomized male mice compared with intact male mice [45].

Figure 2. Hypothalamus–pituitary–gonadal axis and effects of gonadal steroids on the immune system. Whereas T mainly has anti-inflammatory effects, the effects of E are complex. Solid arrows represent stimulation, dashed arrows represent inhibition.
E: Estrogen; FSH: Follicle-stimulating hormone; GnRH: Gonadotropin-releasing hormone;
LH: Luteinizing hormone; T: Testosterone.

The mechanisms underlying disease associations with testosterone levels may be understood through studies of related hormones. Gonadotropins have been found to be altered in male RA patients compared with controls with diverse results [46,47]. Tengstrand *et al.* found low levels of luteinizing hormone in male patients compared with controls, even though testosterone

levels were low, indicating a central dysfunction of the HPG axis [47]. Gordon *et al.*, however, found opposite results, with high levels of luteinizing hormone [46], which is more compatible with a primary gonadal failure.

Hormone-related predictors of RA
■ Women
Oral contraceptives (OCs), breast feeding, parity, age at menarche and age at menopause have all been suggested to influence the risk of RA development in women. The available evidence on these hormone-related predictors is summarized in TABLE 1, which also lists key studies in this field.

The first study to suggest that OCs protect against development of RA was published in 1978 [48]. Results have thereafter been diverging, from reports confirming a protective effect to studies not reporting any association [49–51]. These discrepancies may partly be explained by differences between the study populations, in particular in age distributions, proportion of OC users, and type and duration of OC use. Studies of healthy women have suggested that OC use may be associated with a lower prevalence of rheumatoid factor (RF) in the general population [52]. Several studies have found that OC use is associated with a milder type of RA with less disability, measured by the Stanford Health Assessment Questionnaire [53,54].

During pregnancy, reduced disease activity is seen in many women with RA [55], in particular those who are ACPA negative [56]. Possible explanations include a shift in the maternal immune system from Th1- to a more Th2-based defence and/or an increased number of Tregs [57]. Several epidemiological studies have found parity to protect against RA [58,59], although some inconsistent results have been reported [60,61]. Discrepancies may be explained by differences in age and in the time that had elapsed since prior pregnancies. A recent study demonstrated a strong protective effect of parity for RA with onset before age 45 years, but no significant reduction in disease with later onset [62]. This association was stronger closer to the childbirth [62]. Fetal microchimerism, when fetal cells, possibly featuring protective *HLA* alleles, remain in the mother after the pregnancy have been suggested as an explanation for the protective effect of parity.

On the other hand, there is an increased risk of RA during the postpartum period, possibly due to postponement of RA onset during pregnancy [63]. An association between breast feeding and development of RA shortly after the first pregnancy has been reported [64], suggesting short-term effects of hormonal influences related to breast feeding. On the other hand, several prospective studies, including the US

Table 1. Hormone-related factors suggested to influence the risk of rheumatoid arthritis in women.		
Factor	**Effects**	**Ref.**
Oral contraceptives	Reduced risk of RA, in particular in older studies – conflicting results, ORs ranging from 0.4 to 1.4	[48,50]
	Less severe disease phenotype:	
	– 44 vs 22% with mild disease	[53]
	– Mean adjusted difference in HAQ: -0.21; 95% CI: -0.40 to -0.02	[54]
Breast-feeding	Increased risk of RA during the lactation period:	
	– OR: 2.6; 95% CI: 0.8–7.9, during 9 months postpartum	[63]
	Reduced long-term risk in women with extensive cumulative breast feeding	
	– ≥24 months; RR: 0.5; 95% CI: 0.3–0.8	[65]
	– ≥13 months; RR: 0.5; 95% CI: 0.2–0.9	[51]
Parity	Nulliparity may be a risk factor for RA – conflicting results	[58,61,65]
	Possibly reduced risk with parity for young onset RA:	
	– RR: 0.29; p < 0.001 for those with last birth within 1–5 years	[62]
Age at menarche	Conflicting results	
	Increased	
	– <11 years: RR: 1.9; 95% CI: 0.9–2.4	[60]
	versus reduced	
	– <12 years: OR: 0.3; 95% CI: 0.1–0.8 risk with history of early menarche	[67]
	Increased risk after late menarche (≥15 years; OR: 1.9; 95% CI: 1.2–2.8)	[66]
Age at menopause	Increased risk of RA with early menopause (≤45 years)	
	– OR: 1.9; 95% CI: 1.0–3.7	[67]
	Reduced risk of RA with late menopause (>51 years)	
	– RR: 0.6; 95% CI: 0.4–1.0	[74]
HAQ: Health Assessment Questionnaire; OR: Odds ratio; RA: Rheumatoid arthritis; RR: Relative risk.		

Nurses Health Survey [65] and the Malmö Diet and Cancer Study [51], have found a reduced long-term risk of RA in women with a history of cumulative breast feeding of more than 1 year. This is compatible with distinct effects of breast feeding, which may increase the risk of RA after pregnancy in a small, susceptible group of individuals, and have long-term immunomodulatory effects that reduce the risk of women developing RA in their 40s or later.

A Danish case–control study of 366 women found that those with a history of late menarche (≥15 years) had an almost doubled risk of RA compared with those who had menarche at 12 years of age or less [66]. In a nested case–control study, based on incident cases and matched controls from the prospective Malmö Diet and Cancer Study cohort, early menarche, defined as menstrual periods occurring before the age of 12 years, was associated with a significantly reduced risk of RA (FIGURE 3) [67]. This is in contrast to an American prospective study, which reported a nonsignificant opposite trend, where females who entered menarche before the age of 11 years had a higher risk of RA compared with those with menarche at ≥13 years of age [60]. These discrepancies may be explained by geographic or ethnic differences or by uncertainties based on the limited number of individuals with early menarche.

Menopause is defined as cessation of a woman's menstrual periods [68]. Naturally occurring menopause before the age of 40 years is referred to as premature ovarian failure [69]. Early menopause, often defined by menopause before the age of 45 years [70], is a predictor of several autoimmune diseases, such as systemic lupus erythematosus [71], Type 1 diabetes [72] and giant cells arteritis [73]. A prospective cohort study from Iowa (USA) showed that women with menopause after the age of 51 years had a relative risk of 0.64 to develop RA compared with women with menopause before the age of 45 years [74]. In analyses of the Malmö Diet and Cancer Study, we found that early menopause, occurring at the age of <46 years, was associated with an increased risk of future development of RA [67]. This association remained statistically significant in multivariate conditional logistic regression adjusted for duration of breast feeding, age at menarche, smoking and level of formal education (FIGURE 3). In analyses stratified by RF status at RA diagnosis or later, a stronger association was seen for early menopause with RF-negative RA compared with RF-positive RA [67]. Based on further studies of this sample of 136 incident female cases of RA,

using cluster analyses of clinical outcome data, we reported that a history of early menopause was mainly associated with development of a mild/moderate phenotype of RA, with a relatively low proportion with classic radiographic damage and on average limited disability after 5 years of follow-up [75].

HRT has been used since 1941 to reduce clinical symptoms of menopause. HRT is primarily composed of estrogens, but also progesterone, the latter to diminish the risk of endometrium cancer. In addition to the possible ameliorating effect on established RA [31], as discussed above, it has been suggested that HRT could have a protective effect against development of RA [32], although there are conflicting results indicating a significantly elevated risk of RA in former HRT users compared with nonusers [74].

Finally, androgen levels may be important for the early disease process not only in men, but also in women. However, a prospective study of female pre-RA cases found no evidence of lower androgen levels, measured at a single time point prior to RA onset, compared with matched controls [76]. In addition, there were no associations between polymorphisms in sex hormone receptors and the risk of RA [76].

■ Men
Androgens have been suggested to influence the risk of RA development in men. Evidence implicating a protective effect of testosterone is summarized in TABLE 2, which also lists key studies in this field. Most of this is circumstantial, including studies of patients with established RA and mechanistic studies using *in vitro* models
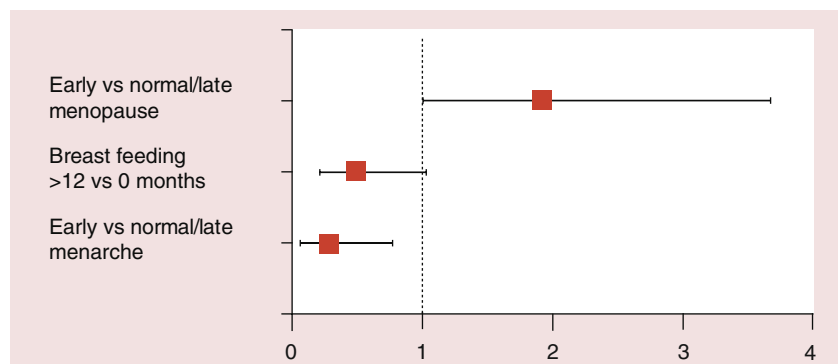
Figure 3. The impact of a history of early menopause (at age <46 vs ≥46 years), long-term breastfeeding (cumulative >12 vs 0 months, regardless of number of children) and early menarche (<12 vs ≥12 years) on the risk of developing rheumatoid arthritis in the Malmö Diet and Cancer study. Multivariate analyses, adjusted for all three variables, smoking and level of formal education. Odds ratios with 95% CIs are depicted. The area to the right of the referent number 1 indicates an inreased risk, whereas the area to the left indicates a decreased risk.
Data taken from [67].

and animal models (see the sections 'Effects of gonadal steroids in RA' and 'Immunoregulatory role of gonadal steroids' above). To our knowledge, only three prospective studies, two of which included men, on the impact of androgen levels on the future risk of RA have been conducted [76–78]. The first study investigated incident cases of RA in a cohort based on health surveys in four regions of Finland in 1973–1977. In a nested case–control study, the 32 incident male RA cases did not have any significant differences in testosterone levels prior to RA onset compared with controls [77]. However, this study did not adjust for potential confounders and had limited power for stratification by different phenotypes of RA. The second study was based on the Malmö Preventive Medicine Program, a population-based health survey performed in Malmö (Sweden) in 1974–1992 [78]. In analyses of 104 male incident cases of RA, we found that individuals who subsequently developed RF-negative RA had lower testosterone levels compared with matched controls. In conditional logistic regression analysis, adjusted for smoking, BMI and socioeconomic status, there was a significant negative association between testosterone and future RF-negative RA (Figure 4). There was a similar trend for RF-positive RA, but this did not reach statistical significance (Figure 4). Results were similar for free testosterone [78], calculated from total testosterone and sex-hormone binding globulin levels using the Vermeulen formula [79].

The median time from inclusion in the Malmö Preventive Medicine Program to RA diagnosis in this sample was 12.7 years [78]. To exclude nascent inflammation in pre-RA cases as an explanation for the differences in testosterone levels, additional analyses were limited to the cases that were diagnosed with RA more than 5 years after screening, with similar results [78]. Furthermore, baseline erythrocyte sedimentation rates were not different in cases and controls, again suggesting that suppression of testosterone due to early RA-related inflammation did not explain these findings.

In the study of testosterone levels in pre-RA cases and controls, we also found discrepancies in follicle-stimulating hormone levels (FSH) levels between RF-negative RA and RF-positive RA, indicating different hormone-related pathomechanisms behind the two subtypes of the disease [78]. FSH levels were higher before onset of RF-negative RA, which is compatible with increased pituitary secretion of FSH due to a hypothalamus-pituitary response to testicular dysfunction. By contrast, lower FSH levels were found before the onset of RF-positive RA, implicating an impaired hypothalamus–pituitary function as a possible factor in the pathogenesis of RF-positive RA.

Taken together with other data of relevance to this issue (Table 2), this prospective study suggests that testosterone may be protective against development of RA in men. Since it was the first major study of testosterone and related hormones

Table 2. Evidence suggesting a protective role of testosterone for rheumatoid arthritis development in men.

Study (year)	Research method	Finding	Ref.
Humphreys *et al.* (2012); Araujo *et al.* (2011); Wu *et al.* (2010); Myaseodova *et al.* (2010)	Epidemiologic studies of the age- and sex-specific incidence of RA	Increasing risk of RA in men >60 years of age (Figure 1) – parallel to reduced testosterone levels	[2,3,6,7]
Cutolo *et al.* (1988); Spector *et al.* (1989)	Cross-sectional studies of men with established RA	Lower testosterone levels compared with controls	[38,39]
Tengstrand *et al.* (2009)	Cross-sectional study of men with recently diagnosed RA	Lower free testosterone levels compared with controls	[37]
Cutolo *et al.* (1991); Hall *et al.* (1996); Booji *et al.* (1996)	Controlled trials of testosterone supplementation in men and women with established RA	Some studies suggest a beneficial effect on disease activity of testosterone – conflicting results	[42–44]
Janele *et al.* (2006)	*In vitro* studies of stimulated human peripheral blood leukocytes	Testosterone reduced secretion of proinflammatory cytokines	[20]
Keith *et al.* (2013)	Studies of effects of orchidectomy in the SKG arthritis mouse model	Absence of testosterone led to increased arthritis, as well as increased extra-articular lung involvement and increased autoantibody production	[45]
Pikwer *et al.* (2013)	Prospective study of risk factors for development of RA, using a population-based health survey	Negative association between testosterone levels and subsequent development of RF-negative RA, adjusted for smoking, BMI and socioeconomic status (Figure 4)	[78]
RA: Rheumatoid arthritis; RF: Rheumatoid factor.			

in the preclinical phase of RA, these findings should be verified in other populations.

## Role of confounders in analyses of hormone-related predictors

In analyses of hormones and hormone-related predictors of RA, a number of potential confounders need to be taken into account. For example, smoking is an established risk factor for RA [80], and it is also known to affect hormonal factors. Smoking is associated with increased risk of early menopause [81]. Furthermore, a low level of formal education is a predictor for RA [80], as well as many other chronic diseases [82], and also for early menopause [81]. However, in the analyses based on the incident RA cases from the Malmö Diet and Cancer Study, the association between early menopause and RA remained significant in models adjusted for current smoking and level of formal education (FIGURE 2).

Smoking is also known to affect androgens, with higher testosterone levels reported in men who smoke [83]. This means that analyses that do not adjust for smoking may fail to detect a true association between low testosterone levels and RA. In addition, obesity, in particular visceral and abdominal fat, is known to be associated with low testosterone levels [84], probably due to increased conversion of androgens to estrogen in the adipose tissue [85]. In the study of testosterone and risk of RA in the Malmö Preventive Medicine Program, there was a trend towards a negative association between BMI and subsequent RA [78]. Smoking and BMI both had a significant impact on testosterone levels in this sample [78]. Furthermore, socioeconomic status (defined as blue- vs white-collar worker status, based on current occupation) also appeared to affect testosterone, with a trend towards higher levels among blue-collar workers [78]. Therefore, the analysis was adjusted for smoking, BMI and socioeconomic status (FIGURE 4). Similar findings were obtained in models that did not include socioeconomic status as a covariate [78].

Finally, a number of different comorbidities have been shown to be associated with low testosterone levels [86]. In the Malmö study, the proportions with self-reported cardiovascular disease, diabetes or cancer were low, without major differences between pre-RA cases and controls [78]. Approximately 70% in both groups reported that they considered themselves to be in full health.

Body fat, testosterone & RA

As mentioned above, the relation between testosterone levels and RA development in men seems
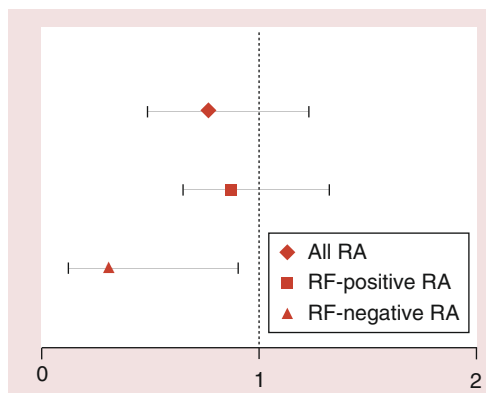
Figure 4. The impact of serum testosterone levels on future development of rheumatoid arthritis in male participants in the Malmö Preventive Medicine Project, by rheumatoid factor status at diagnosis or later. Multivariate analyses, adjusted for smoking, BMI and socioeconomic status. Odds ratios with 95% CIs are depicted. The area to the right of the referent number 1 indicates an inreased risk, whereas the area to the left indicates a decreased risk.
RA: Rheumatoid arthritis; RF: Rheumatoid factor.
Data taken from [78].

to be influenced by BMI. It is, therefore of particular interest that BMI may have sex-specific effects on the risk of RA.

In a recent case–control study, based on an inception cohort of patients with early RA from central Sweden, Wesley *et al.* reported a negative association between obesity and ACPA-positive RA in men [87]. By contrast, in women there was no association between ACPA-positive RA and obesity, whereas women who developed ACPA-negative RA were more likely to be obese, compared with controls [87].

Several previous studies have also indicated that a high BMI is a predictor of RA in women, including a retrospective survey of a population-based cohort of patients with RA from Olmsted County [88]. In that study, obesity was also associated with increased risk of RA in men, but the estimated impact of increasing obesity on the incidence of RA was considerably greater in women [88]. Changes in the prevalence of obesity over time, as well as geographic differences in other exposures related to high BMI, may partly explain the differences between studies performed in different countries.

The authors recently reported preliminary data on the total sample of incident RA cases in the Malmö Preventive Medicine Program [89], not limited to male subjects with blood samples available for testosterone analyses. In analysis of 151 men and 139 women, with matched

controls, the authors found that BMI did not affect development of RA in women, whereas in men, a high BMI was associated with a reduced risk of RA [89]. Adjustment for smoking had no major effect on the negative association between BMI and RA development in men.

Taken together with the previously discussed findings on testosterone and RA development in men, these results suggest that in men with a relatively low BMI, low testosterone level is an indication of increased risk of RA. By contrast, low testosterone in a man with a high BMI, likely due to aromatization in adipose tissue, does not have the same implication. It follows that adipose tissue may be involved in mechanisms that are protective from RA, and independent of testosterone.

Conclusion

The sex-specific patterns in incidence rates of RA in men and women suggest that hormone-related factors play a role in disease development. Prominent hormonal changes, such as menopause at an early age in women and a significant drop in testosterone in men, seem to predict RA, in particular RF-negative RA with disease onset in older individuals. Long-term breast feeding and an early menarche are associated with a reduced risk of RA, suggesting that a long reproductive period may be protective of RA in women. The concept of an association between low testosterone and development of RA is supported by several lines of evidence, including a recent animal

model study of orchidectomized arthritis mice, and a recent prospective study of pre-RA cases and controls. In that type of studies, the role of confounders, such as smoking, and sex-specific effects of some exposures, such as BMI, need to be taken into account. Substitution with estrogen in women and with testosterone in men may be useful as treatment for RA, although data are limited and somewhat conflicting.

Future perspective

Over the next 5–10 years, work will focus on understanding the heterogeneity of RA, and the underlying mechanisms. Hormone-related factors may be relevant to disease development and disease expression in a particular subset of patients, which may be identified using studies of biomarker patterns. This can be applied to patients with early disease, to high-risk individuals with possible early symptoms of RA, and to population based cohorts that are followed with the aim of identifying incident cases for nested case–control studies of risk factors for RA. Such studies, as well as further work on the role of testosterone and other sex hormones in animal arthritis models, may be used as a basis for controlled trials of hormone substitution as treatment or prevention of RA. For this, collaboration within national and international networks is extremely important. In addition, the gut hormones–cytokine networks also play key roles in regulating the immune system [90], and studies of interactions between different endocrine

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Executive summary

Epidemiology of rheumatoid arthritis: sex-specific patterns
- The peak incidence of rheumatoid arthritis (RA) in women is observed in the postmenopausal period.
- In men, the incidence of RA increases after 60 years of age, parallel to reduced testosterone levels.

Sex differences in the RA phenotype
- Among RA patients, men have higher rates of severe extra-articular disease, and women have higher rates of orthopedic surgery.
- Female patients with RA have worse self-reported outcomes and are, therefore, less likely to obtain clinical remission.

Immunoregulatory role of gonadal steroids
- Estrogen has diverse effects on the immune system, but the net effect seems to anti-arthritic in animal models.
- Testosterone mainly has immunosuppressive and anti-inflammatory effects.

Effects of gonadal steroids in RA
- Hormone replacement therapy may lead to clinical improvement in women with RA, although results are conflicting.
- Testosterone levels are lower in men with early RA and established RA compared with controls.
- Recent data from animal studies support a protective role for testosterone against RA.
- There are limited data on treatment with testosterone for RA.

Hormone-related predictors of RA
- Early menopause is a predictor of RF-negative RA with a relatively mild phenotype.
- Long-term breast feeding and early menarche may be protective against RA.
- A recent prospective study demonstrated a negative association between testosterone levels and the risk of RF-negative RA.
- The associations between hormone-related factors and RA are affected by exposures such as smoking and BMI.

pathways may provide further understanding of the pathogenesis of RA.

Changes in hormone-related exposures may affect trends in RA occurrence. For example, the global trend towards increasing rates of breast feeding may contribute to a reduced incidence of RA, although such trends are rapidly changing and complicated by underlying associations with socioeconomic factors. Furthermore, the worldwide epidemic of obesity may also affect hormonal factors related to RA, and influence disease occurrence, disease phenotype, treatment and comorbidities. Studies should be designed with the aim of forming an evidence base for the impact of life style modification on each of these aspects.

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1. Which of the following statements regarding the gender-based epidemiology and clinical consequences of rheumatoid arthritis (RA) is **most** accurate?

☐ **A** The overall risk for RA is similar among both women and men

☐ **B** RA most commonly occurs among men younger than 45 years

☐ **C** Men have a lower risk for extra-articular manifestations of RA compared with women

☐ **D** Women have worse patient-reported outcomes compared with men

2 Which of the following statements regarding the relationship between changes in sex hormone levels and RA among men is **most** accurate?

☐ **A** Lower testosterone levels have been associated with a higher risk for incident rheumatoid factor (RF)-negative RA

☐ **B** Follicle-stimulating hormone (FSH) levels have not been associated with incident RF-negative RA

☐ **C** FSH levels are increased among men in whom RF-positive RA develops

☐ **D** A low body mass index is protective against incident RA among men with low testosterone levels

3   Which of the following statements regarding hormonal treatment and RA is **most** accurate?

☐ **A**   Hormone therapy usually results in worsened RA symptoms

☐ **B**   Hormone therapy can worsen the risk for cardiovascular disease among women with RA

☐ **C**   Large clinical trials have demonstrated that testosterone treatment relieves RA symptoms among men

☐ **D**   Oral contraceptives have no effect on the severity of RA