

# Sex-specific differences in the prevalence, clinical presentation and prognosis of rheumatic autoimmune diseases

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# Sex differences in rheumatic autoimmune diseases

1. Which diseases?
2. Who?
3. Why?
4. Does it matter?



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# What diseases are autoimmune?

## Single-organ

- **Skin:** psoriasis\*, epidermolysis bullosa, pemphigus, etc.
- **Thyroid:** autoimmune thyroiditis (Grave's disease, Hashimoto)
- **Pancreas** (endocrine): type I Diabetes mellitus
- **Liver:** autoimmune hepatitis, primary biliary cholangitis
- **Gut:** inflammatory bowel disease\*, atrophic gastritis
- **Nervous system:** multiple sclerosis, myasthenia gravis, etc.
- **Eye:** autoimmune uveitis\*
- **Kidney:** Goodpasture syndrome
- \*often associated with systemic autoimmune disease

## Systemic = "rheumatic"

- **Connective tissue diseases (CTDs)**
  - Systemic lupus erythematosus
  - Autoimmune inflammatory myopathies
  - Systemic sclerosis
  - Sjögren's Syndrome
  - Mixed connective tissue disease
  - Undifferentiated CTD
- **Systemic vasculitis**
  - Giant cell arteritis
  - Polyarteritis nodosa
  - ANCA-associated vasculitis
  - Small vessel vasculitides
- **Inflammatory Arthritis**
  - Rheumatoid arthritis
  - Spondyloarthritis, including psoriatic arthritis

# Rheumatoid arthritis



Rheumatoid arthritis  
(late stage)

Boutonniere  
deformity  
of thumb

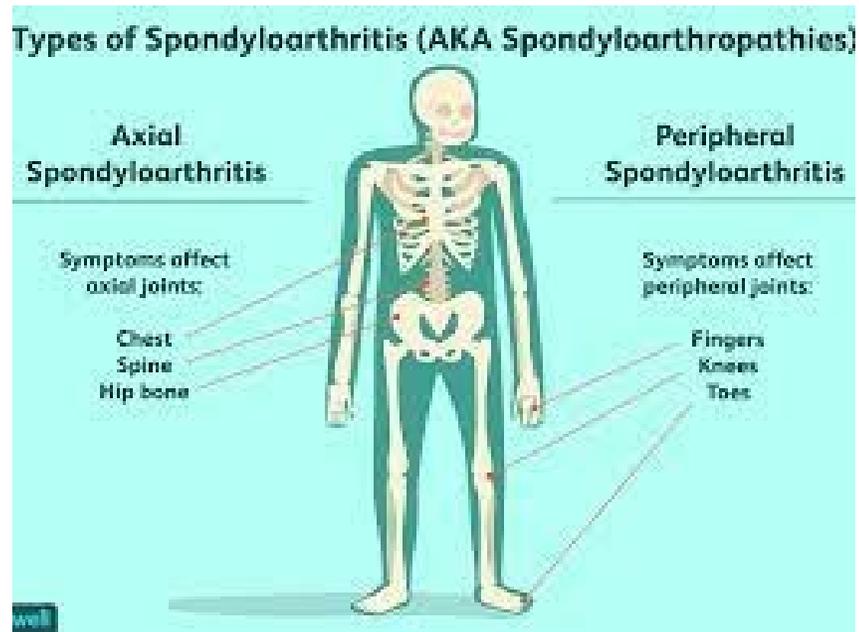
Ulnar deviation of  
metacarpophalangeal  
joints

Swan-neck deformity  
of fingers

ADAM.

- affects predominantly small joints in hands and feet
- large joints can be involved too
- symmetrical involvement
- specific serologic markers: rheumatoid factor, anti-citrullinated protein antibodies
- erosive disease (X-rays)
- untreated may lead to severe deformities and disability

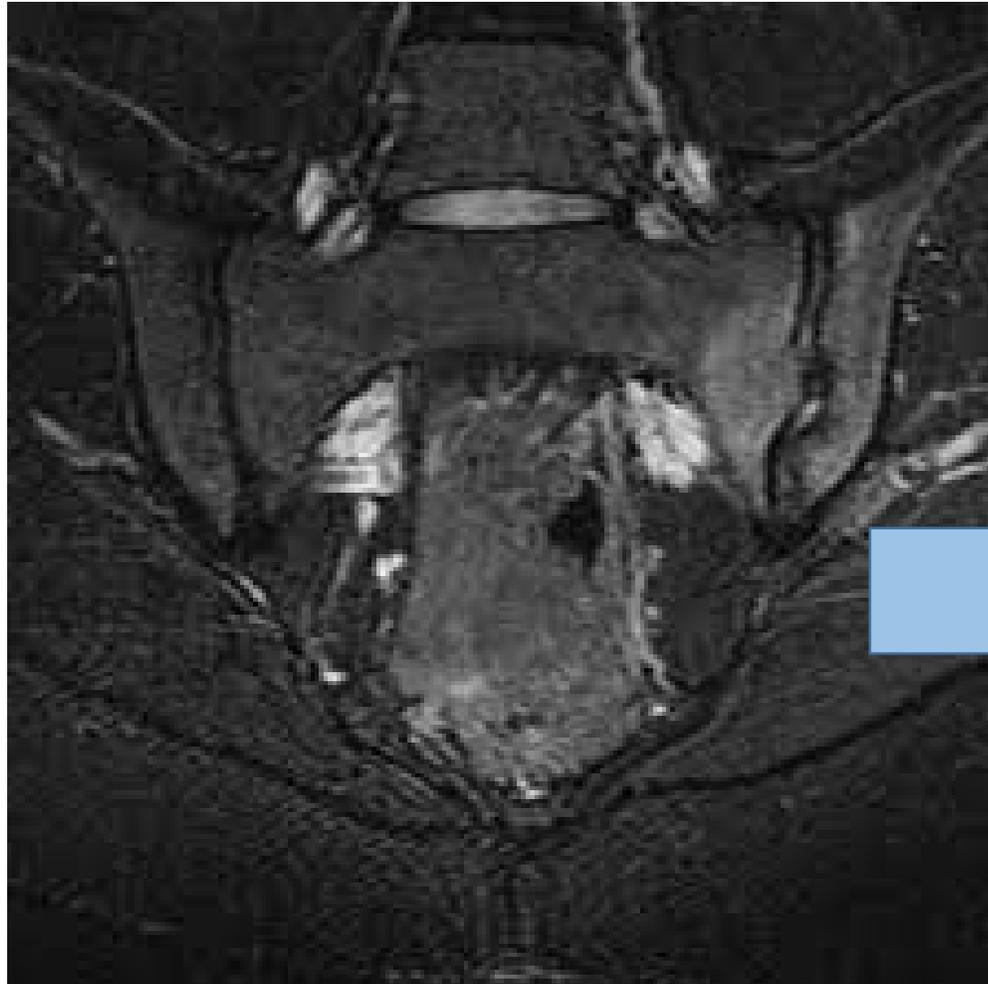
# Spondyloarthritis (SpA)



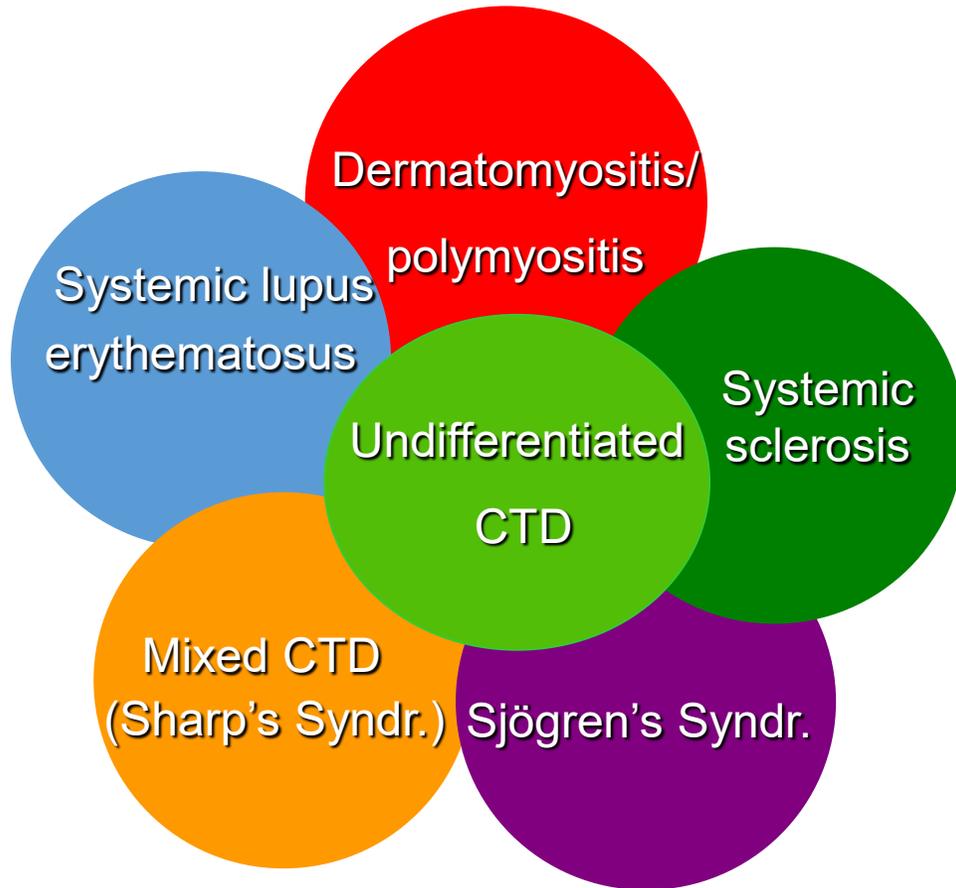
Spectrum of sero-negative arthritides  
(no specific auto-antibodies)

- involve the axial skeleton
- large joints can be involved too
- asymmetrical involvement
- imaging: MRI more sensitive than x-rays
- hallmark: sacroiliac joint involvement

# axSpA: sacroiliitis, MRI vs. x-ray



# The spectrum of Connective Tissue Diseases (CTD)

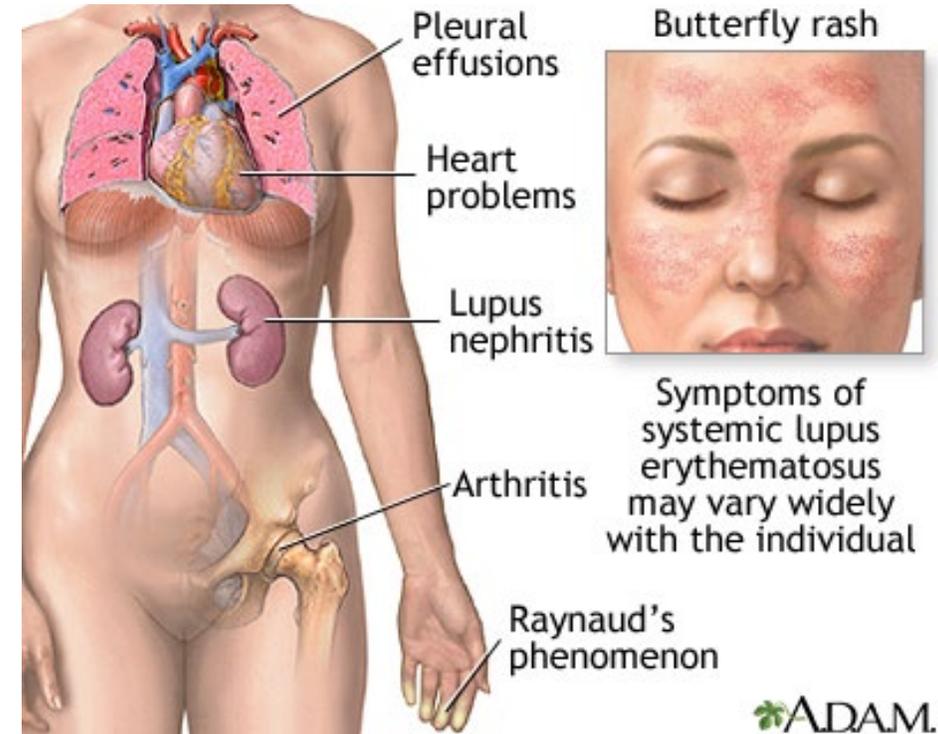


## CTD: disease group sharing aetiopathogenic, serologic and clinical features

- Autoimmune pathogenesis
- Antinuclear antibodies (ANA)
- Articular, mucous, cutaneous involvement
- Internal organ involvement
- Raynaud's Phenomenon

# Systemic lupus erythematosus (SLE)

- Driven by humoral autoimmunity
  - disease-specific autoantibodies
- Clinical manifestations:
  - Systemic e.g. fever
  - Cutaneous
  - Articular
  - Haematologic
  - Serositis
  - Nephritis
  - Nervous system etc.



# Systemic sclerosis (SSc)

- microvasculopathy & fibrosis
  - disease-specific autoantibodies
- Clinical manifestations:
  - Raynaud's phenomenon
  - Finger ulcers
  - Skin fibrosis
  - Arthritis & joint contractures
  - Lung fibrosis
  - Pulmonary hypertension
  - Gastro-intestinal tract dysmotility
  - Heart involvement
  - Renal crisis etc.



# Sjögren Syndrome (SS)

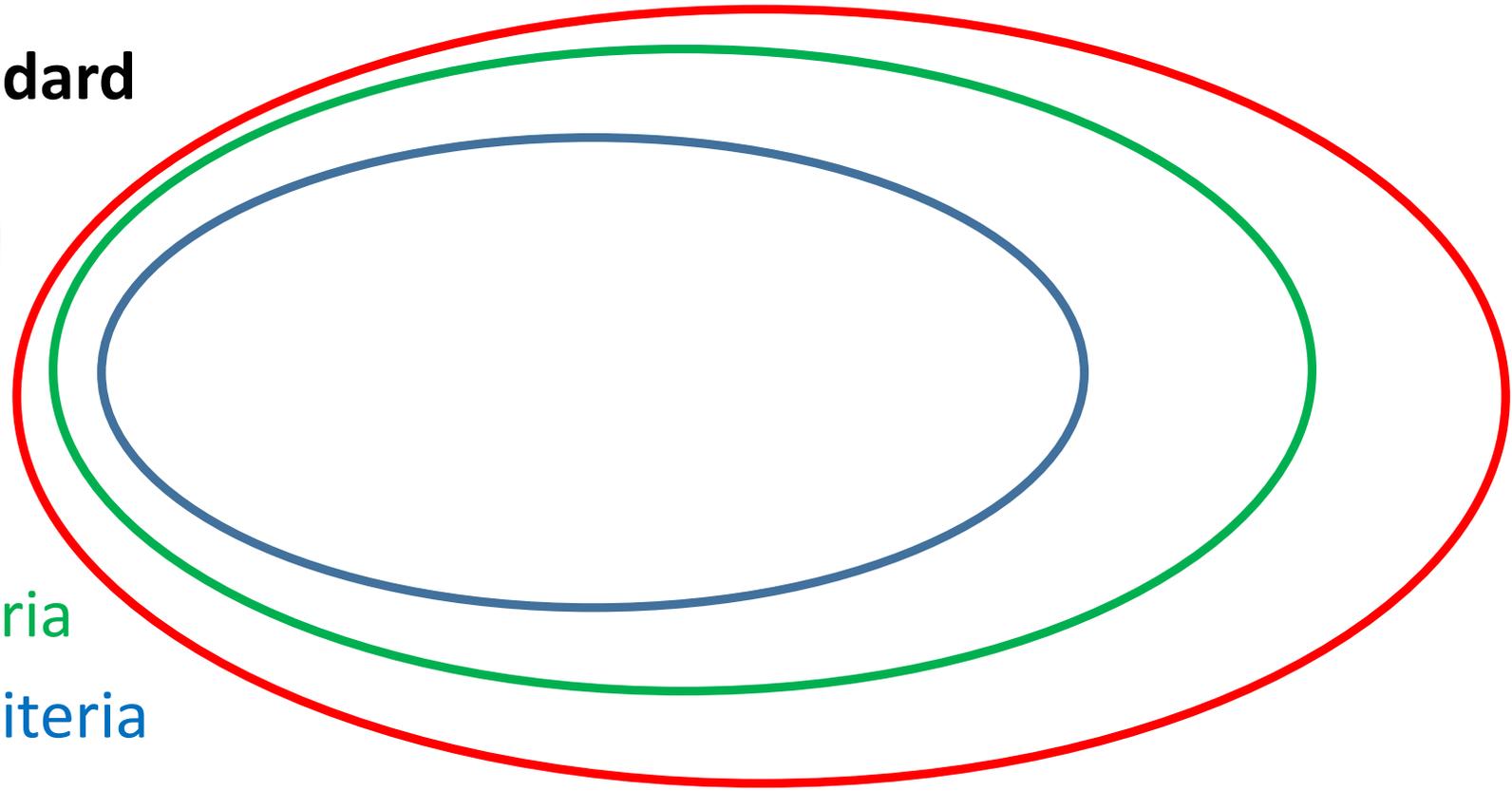
- Inflammation of exocrine glands
  - disease-specific autoantibodies
- Clinical manifestations:
  - Dry eyes
  - Dry mouth
  - Dryness of airway mucosa
  - Parotid enlargement
  - Arthritis
  - Small vessel vasculitis
  - Renal & lung involvement
  - May lead to lymphoma



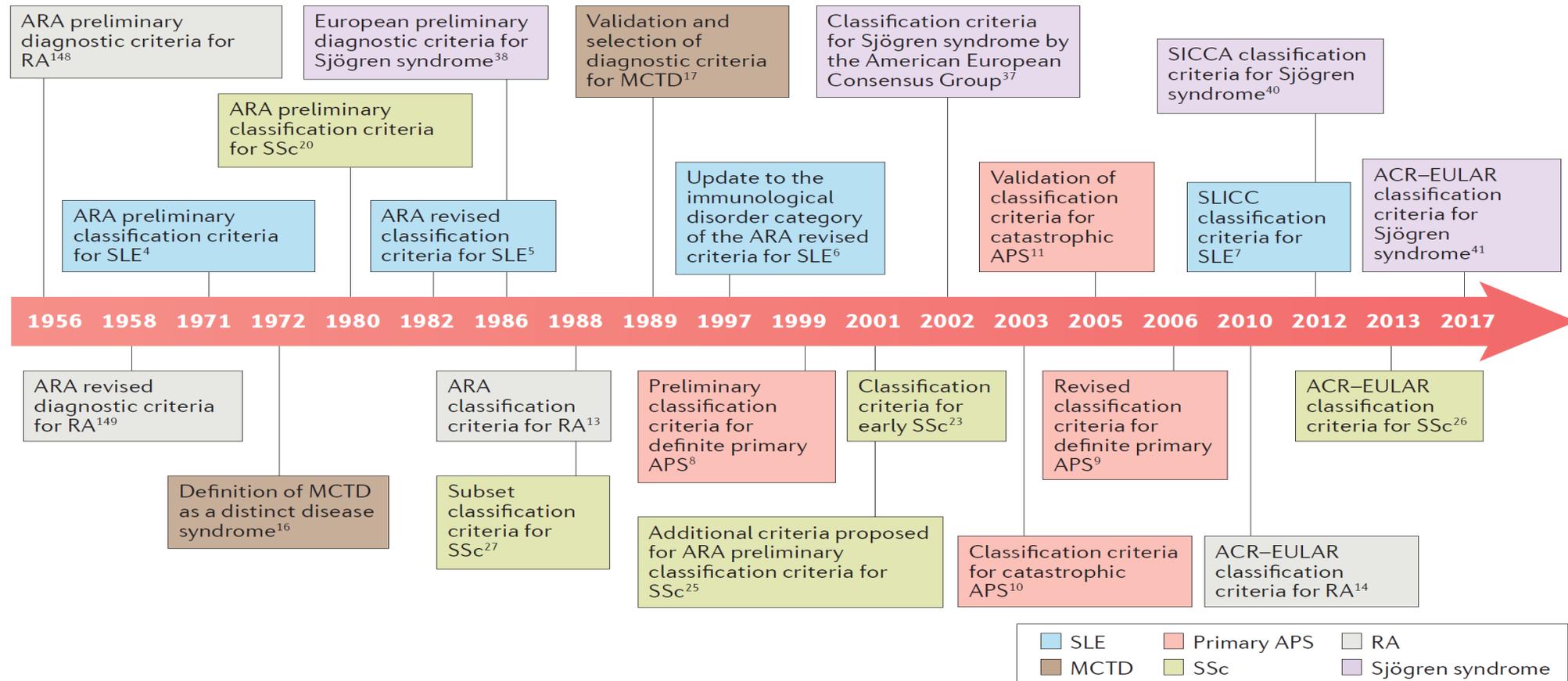
# Classification vs. diagnosis criteria

To date, **gold standard**  
for rAID diagnosis  
is **expert opinion!**

- Disease
- Diagnostic criteria
- Classification criteria



# Historical evolution of the clinical classification and diagnostic criteria for rheumatic autoimmune diseases (rAIDs)



Barturen, G *et al.* Moving towards a molecular taxonomy of autoimmune rheumatic diseases. *Nat Rev Rheumatol* **14**, 75–93 (2018).

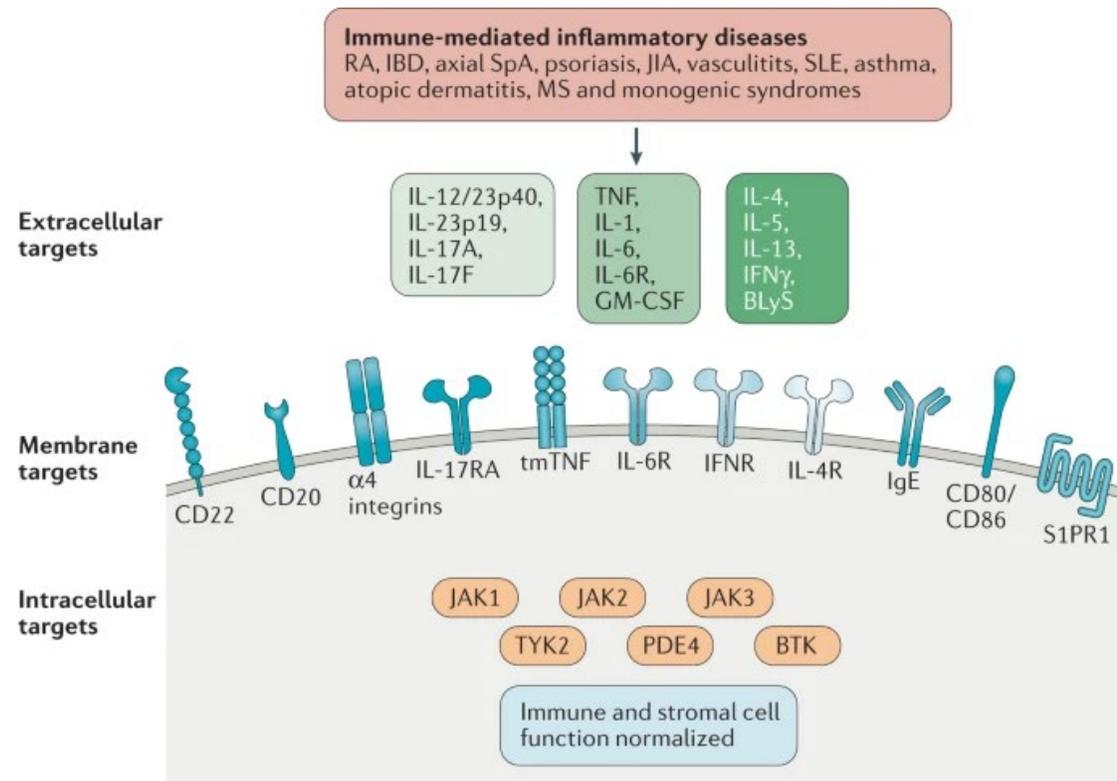
# Immune-mediated inflammatory diseases (IMIDs)

- IMIDs include rAIDs but also other autoimmune diseases:
  - **arthritis: rheumatoid arthritis (RA) & the spondyloarthritis (SpA) disease spectrum**
  - **connective tissue disorders (CTDs)**
  - cutaneous inflammatory conditions (e.g. psoriasis and atopic dermatitis)
  - inflammatory bowel disease
  - asthma
  - autoimmune neurological diseases e.g. multiple sclerosis
- common pathogenetic features = ‘public’ immune pathways
- unique (‘private’) pathways defining the clinical phenotype, tissue localization and therapeutic response profile

McInnes, I.B., Gravalles, E.M. Immune-mediated inflammatory disease therapeutics: past, present and future. *Nat Rev Immunol* **21**, 680–686 (2021).



# Why IMIDs? Common molecular therapeutic targets

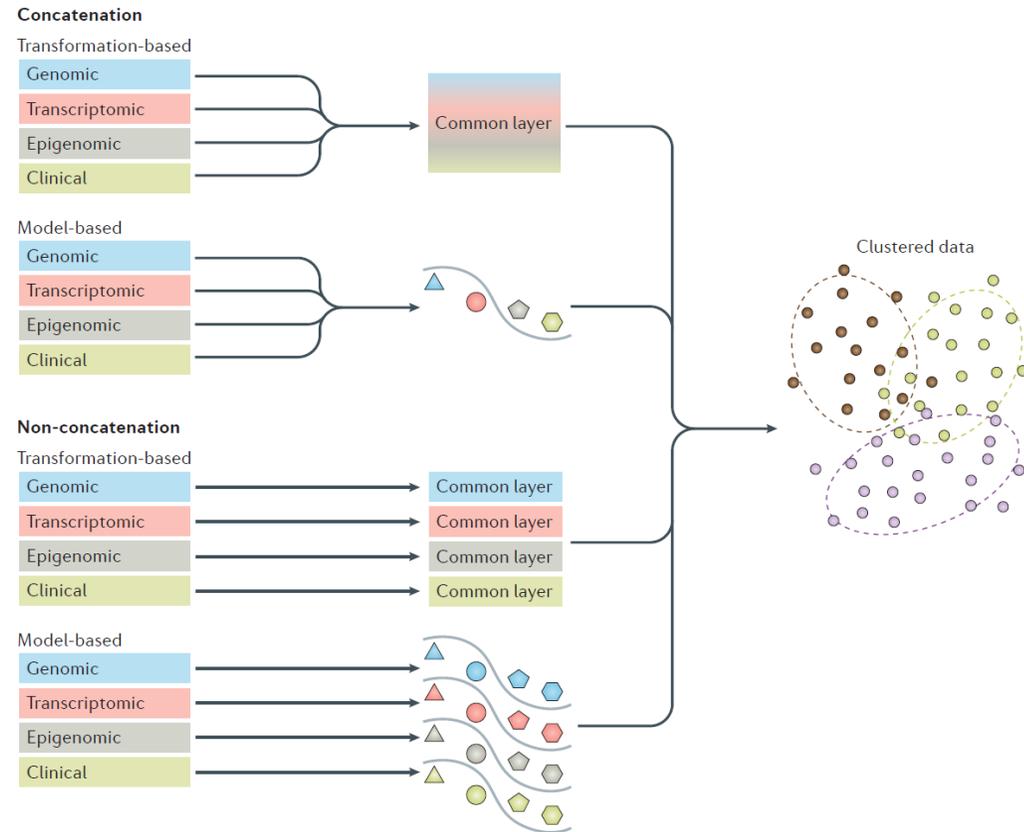


Key targets in IMIDs for biological and small-molecule therapies

- extracellular
- membrane-bound
- intracellular

McInnes, I.B., Gravalles, E.M. Immune-mediated inflammatory disease therapeutics: past, present and future. *Nat Rev Immunol* **21**, 680–686 (2021).

# Towards a molecular taxonomy of rAID



- Current rAID classification criteria are based on expert opinion (pattern recognition)
- rAID share molecular disease pathways
- Discriminating between diseases by comparing molecular profiles is feasible
- Precision medicine of rAID should start with a robust molecular classification and the identification of biomarkers

Barturen, G *et al.* Moving towards a molecular taxonomy of autoimmune rheumatic diseases. *Nat Rev Rheumatol* **14**, 75–93 (2018).

# Sex differences in rheumatic autoimmune diseases

## 1. Which diseases?

**accumulation of knowledge changes the concepts**

- better (earlier) diagnosis
- more efficacious treatment

## 2. Who?

## 3. Why?

## 4. Does it matter?

# Sex differences in rheumatic autoimmune diseases

1. Which diseases?

2. Who?

3. Why?

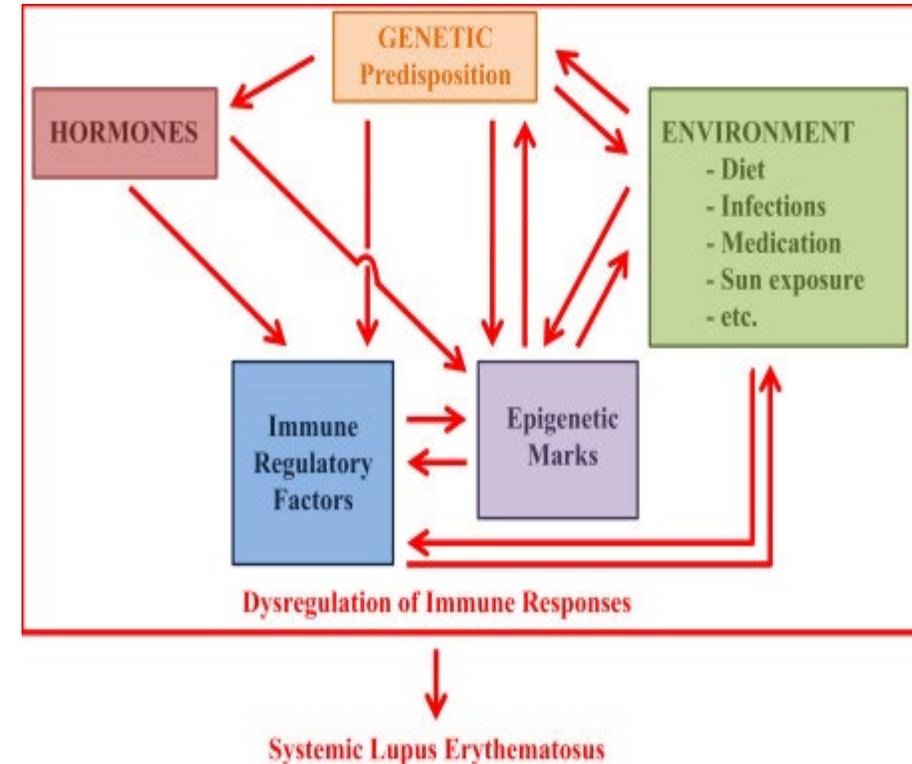
4. Does it matter?



# Who develops autoimmune diseases, and how?

## Pathogenesis of the rAIDs

- Genetic predisposition
    - MHC I, MCH II
    - Other genes
  - Environmental factors
    - Infections
    - Medication
    - Sun exposure
- => Immune dysregulation => disease



# Sex ratios for rheumatic autoimmune diseases

Disease	Female:male ratio	Peak age at onset
Rheumatoid arthritis	2:1 to 3:1	Forties
Systemic lupus erythematosus	9:1	Late teens to early forties
Systemic sclerosis	4:1	Forties
Sjögren's syndrome	15:1	Fifties
Dermatomyositis	2:1	Fifties
Axial spondyloarthritis	1:1	Twenties

***Autoimmune diseases of all organ sites and systems affect ca. 5-8% of the general population, of which almost 80% women***

1. Oliver JE, Silman AJ. Why are women predisposed to autoimmune rheumatic diseases? *Arthritis Res Ther.* 2009; 11(5):252.
2. Jacobson DL, Gange SJ, Rose NR, Graham NM. Epidemiology and estimated population burden of selected autoimmune disease in the United States. *Clin Immunol Immunopathol.* 1997;84:223–43.

# Sex differences in spondyloarthritis

Myth: “axial Spondyloarthritis (axSpA) is a predominately male disease”

- Male : female ratio

- ca. 1950: 10 : 1

- ca. 1990: 3 : 1

- 2016: axSpA in Switzerland 1.03 : 1

- differences are due to method of diagnosis (x-ray vs. MRI) and to changes in the SpA concept / SpA classification criteria

Truth: diagnoses of axSpA are often missed or misdiagnosed in female patients

# Sex differences in rheumatic autoimmune diseases

1. Which diseases?

2. Who?

**RAIDs are definitely more frequent in women**

**However, sex ratios vary among diseases and there are phenotypic differences among sexes**

3. Why?

4. Does it matter?

# Sex differences in rheumatic autoimmune diseases

1. Which diseases?

2. Who?

**3. Why?**

4. Does it matter?



# Why are there sex differences in rAIDs?

- **Influence of sex hormones**
  - Sex
  - Age and life period (menarche, fertile age, menopause)
  - Pregnancy and breastfeeding
  - External hormone use: oral contraception, hormone replacement in menopause
- **Genetic**
  - Klinefelter's syndrome (XXY) : x14 higher in male SLE patients vs. unselected male population
- **Environmental factors**
  - Smoking
  - Occupational:
    - Heavy physical work
    - Silica dust exposure

# Sex differences in rAIDs due to environmental factors

## Environmental factors: confounding association when unequally distributed among sexes

- Smoking: important in the pathogenesis of ACPA-positive RA
- Occupational:
  - spine ankylosis in axial SpA more frequent in men => ankylosing spondylitis (advanced form of axial SpA) is 8-fold more frequent in men
    - axial SpA diagnosis is delayed in women
- silicone implants: probably NOT associated to RA, SLE and SSc
- vaccines: NOT associated to rAIDs

# Sex differences in rheumatic autoimmune diseases

1. Which diseases?
2. Who?
3. **Why? genetics, hormones and particularities of the immune system, but also differences in exposure to external factors play a role**
4. Does it matter?

# Sex differences in rheumatic autoimmune diseases

1. Which diseases?

2. Who?

3. Why?

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# Sex differences in spondyloarthritis

Myth: “axial Spondyloarthritis (axSpA) is a predominately male disease”

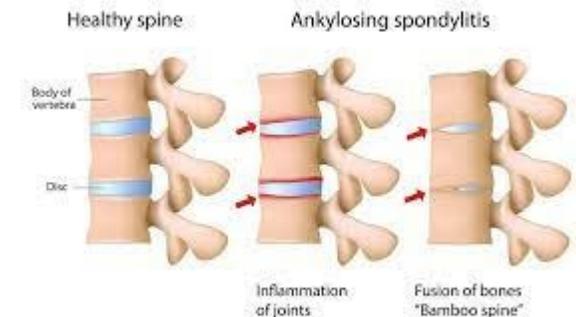
- average delay to diagnosis 6–8 years (all patients)
- delay in diagnosis longer in women: median 9–14y vs 5–7y in men
- widespread pain (ca. 25% female axSpA patients) misdiagnosed as fibromyalgia

Truth: diagnoses of axSpA are often missed or misdiagnosed in females because:

- Women develop less frequently radiographic changes
- Women have more frequently extra-articular manifestations and wide-spread pain

# Sex differences in spondyloarthritis

- Men have a higher radiological progression
  - Occupational factors - mainly heavy physical work- play a role
  - more frequently leading to ankylosis of the spine
- Women have more frequently extra-articular manifestations and wide-spread pain
  - **Diagnostic confusion with fibromyalgia!!!**
- Altogether, the disease burden is similar for both sexes



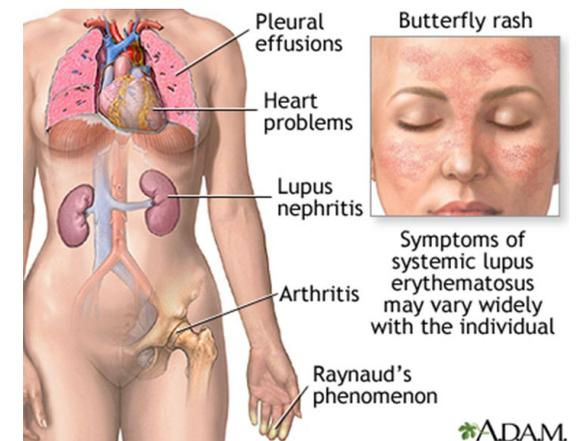
# Sex as a risk factor for worse outcome in SLE

## Men:

- older age at diagnosis and symptom onset
- higher prevalence of nephritis
- more frequent lung complications e.g. pulmonary embolism
- higher disease activity
- higher rate of hospitalization
- higher mortality

## Women:

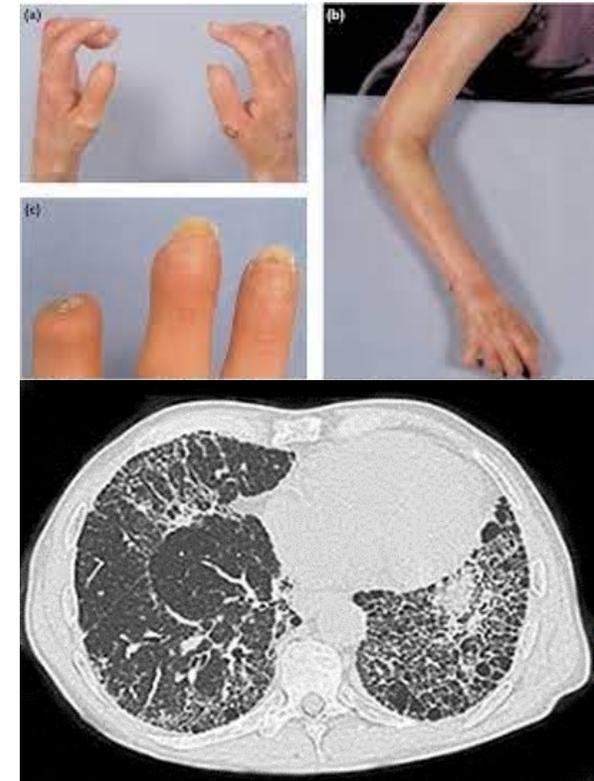
- Pregnancy is associated with disease worsening



# Sex as a risk factor for worse outcome in systemic sclerosis

## Men:

- higher prevalence of diffuse cutaneous involvement
- more frequent digital ulcers
- more frequent lung and heart involvement
- higher mortality
  - younger age at death
  - shorter disease duration at death vs. females



1. Ingegnoli, Ughi & Mihai. Best Pract Res Clin Rheumatol. 2018;32:223-240.

2. Mihai C et al. Ann Rheum Dis 2016; 75:681-6.

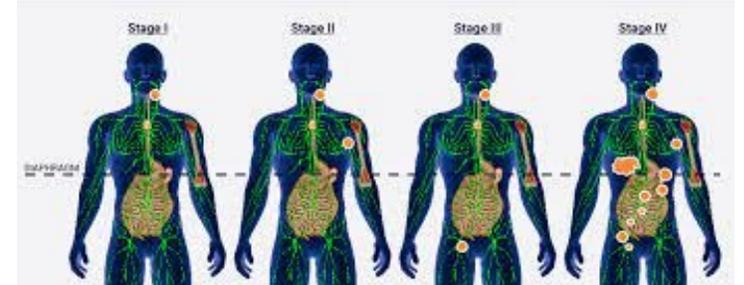
# Sex differences in Sjögren's syndrome (SS)

## Women:

- more frequently depression, fibromyalgia, fatigue

## Men:

- lymphoma more frequently in men
- lymphoma earlier in males than females following SS diagnosis
- mortality 3 times higher in men vs. women in isolated SS



# Why would sex differences in rAIDs matter?

- **sex influences disease susceptibility and clinical presentation**
  - Diagnosis is a synthesis of probabilities!
- **sex is a prognostic factor**
- **family planning:**
  - timing of pregnancy
  - contraception
  - disease management during pregnancy and breastfeeding
  - hormonal replacement
- **response and / or adverse reactions to treatment**

Oliver JE, Silman AJ. Why are women predisposed to autoimmune rheumatic diseases?  
*Arthritis Res Ther.* 2009; 11(5):252.

# Contraception in women with rAIDs

- **Most important issue in SLE**
  - based on disease activity and thrombotic risk (particularly anti-phospholipid antibody [aPL] status)
    - **Intra-uterine devices:** in all patients with SLE and/or anti-phospholipid antibody syndrome (APS), if no gynecological contraindication
    - **combined hormonal contraceptives** can be considered in patients with stable/inactive SLE and negative aPL status
    - **hormonal contraception with progesterone only:** precaution due to risk of thrombosis if positive aPL ± definite APS



Andreoli L, et al. *EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome*. Ann Rheum Dis. 2017; 76:476-485.

# HRT in women with rAIDs

- **important issue in SLE**
  - only for severe vasomotor menopausal manifestations in women with stable/inactive SLE and negative aPL status
  - in patients with positive aPL status: carefully weighed against risk of thrombosis and cardiovascular disease
- **in all other RAIDs** no specific restrictions regarding HRT and contraception



Andreoli L, et al. *EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome*. Ann Rheum Dis. 2017; 76:476-485.

# Sex differences in rheumatic autoimmune diseases

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**YES!!!**

- **sex influences disease susceptibility and clinical presentation**
- **sex is a prognostic factor**

# Take-home messages

**rAIDs have well-known sex differences in disease susceptibility and disease course**

**1. Women are more susceptible to develop rAIDs than men**

- rheumatoid arthritis, systemic lupus, systemic sclerosis, Sjögren

**2. Men often have worse disease course than women in some rAIDs:**

- increased mortality in SLE and SSc
- some symptoms may be worse in women: e.g. fibromyalgia in Sjögren

**3. Sex differences must be taken into account in clinical practice**

- diagnosis, treatment, family planning, pregnancy, hormonal treatment

**Thank you for your attention!**

