



MORTALITY IN INFLAMMATORY RHEUMATIC DISEASES

MAYA MATTAR, MD

ASSISTANT PROFESSOR OF MEDICINE, CASE WESTERN RESERVE UNIVERSITY



A useless life is an early death.

~ Johann Wolfgang von Goethe

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- The background is a dark blue gradient. In the corners, there are decorative white line-art patterns resembling circuit boards or neural networks, with lines connecting to small circles.
- I have no financial disclosures

MORTALITY IN INFLAMMATORY RHEUMATIC DISEASES

- Systemic rheumatic diseases are characterized by increased mortality compared with the general population
- Infection remains the most common cause of death in systemic rheumatic diseases as a result of immunosuppressive treatment and changes in the immune system caused by the disease itself
- Cardiovascular complications are major causes of death, second to infection.
- Organ dysfunction as a result of the disease itself, such as renal failure in patients with SLE or interstitial lung fibrosis with pulmonary hypertension in SSc, is another major cause of reduced survival in systemic rheumatic diseases
- Recent studies, mostly in rheumatoid arthritis and less so in other diseases, have shown that the gap of excess mortality risk is steadily closing.

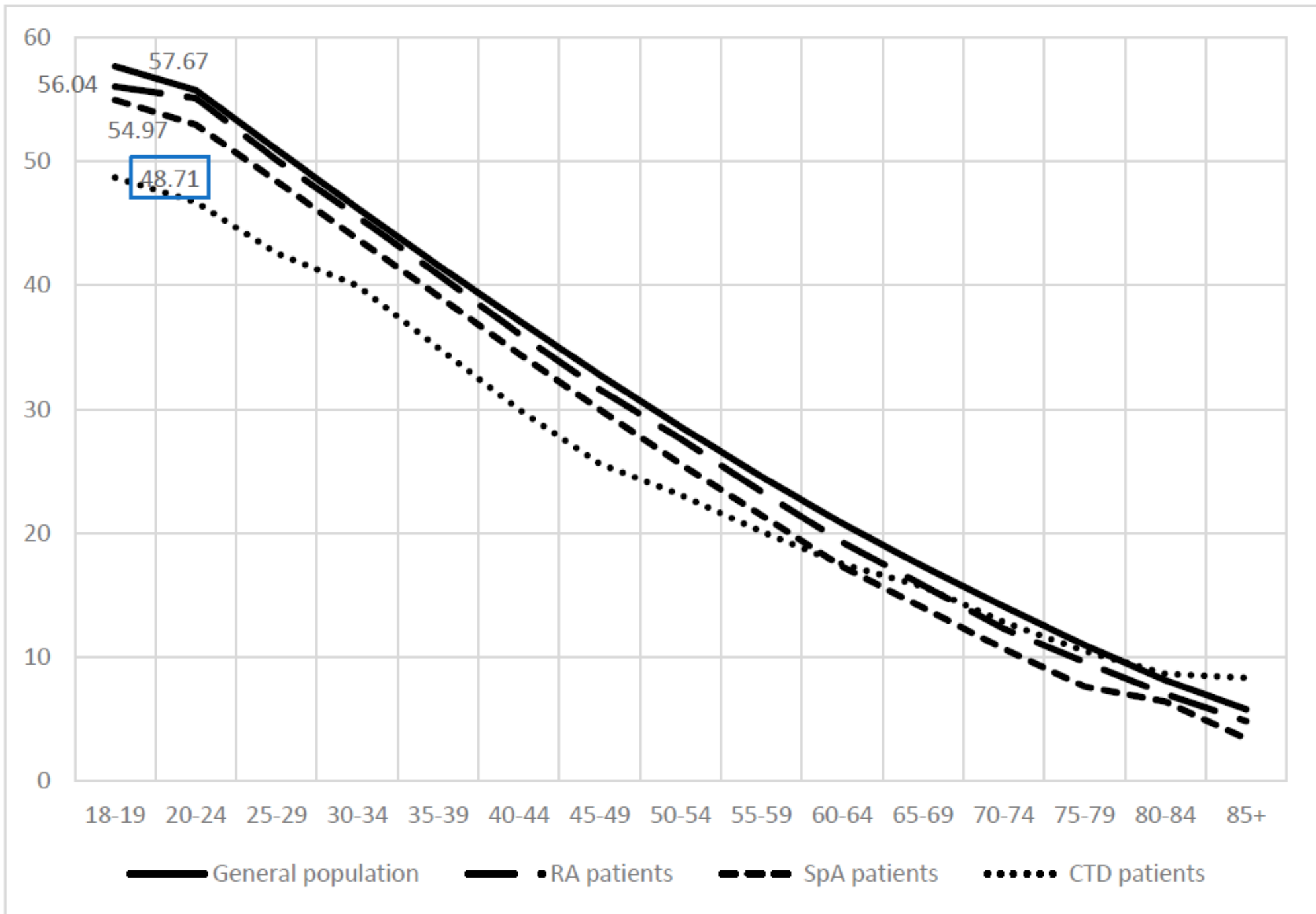
MORTALITY IN INFLAMMATORY RHEUMATIC DISEASES

Characteristic	Rheumatoid Arthritis (<i>n</i> = 6008)	Spondyloarthritis (<i>n</i> = 3289)	Systemic Connective Tissue Diseases (<i>n</i> = 2339)	Total (<i>n</i> = 11,636)
Female no, %	4613 (76.78)	1712 (52.05)	1787 (76.40)	8112 (69.71)
Male no, %	1395 (23.22)	1577 (47.94)	552 (23.60)	3524 (30.29)
Mean age at diagnosis of rheumatic disease (SD)	58.91 (15.01)	48.91 (14.42)	61.37 (17.22)	56.57 (16.08)
Mean years of follow-up (SD)	3.80 (2.04)	3.74 (2.0)	3.38 (2.10)	3.70 (2.05)
Total person years of follow-up	22,861.11	12,303.61	7899.61	43,064.34

MORTALITY IN INFLAMMATORY RHEUMATIC DISEASES

Standardized Mortality Ratios	Rheumatoid Arthritis (M05, M06)	Psoriatic Arthritis (M07)	Ankylosing Spondylitis (M45, M46)	Systemic Lupus Erythematosus (M32)	Sjogren Syndrome (M35.0)	Systemic Sclerosis (M34)	Vasculitis (M30, M31)	Myositis (M33)	Polymyalgia Rheumatica (M35.3)
Total	1.25 (1.14; 1.36)	1.04 (0.81; 1.31)	1.25 (0.88; 1.71)	2.53 (1.59; 3.83)	1.50 (0.98; 2.20)	2.66 (1.49; 4.39)	3.24 (2.59; 4.01)	3.24 (2.59; 4.01)	1.29 (1.07; 1.53)
Women	1.26 (1.13; 1.41)	0.90 (0.56; 1.38)	1.11 (0.48; 2.19)	2.72 (1.64; 4.25)	1.23 (0.72; 1.97)	2.23 (0.82; 4.85)	3.38 (2.42; 4.60)	1.43 (0.30; 4.18)	1.29 (1.03; 1.60)
Men	1.23 (1.05; 1.42)	1.11 (0.83; 1.47)	1.75 (0.36; 5.12)	2.80 (1.03; 6.10)	3.06 (1.40; 5.81)	1.29 (0.87; 1.84)	2.53 (1.16; 4.81)	3.12 (2.28; 4.18)	1.27 (0.93; 1.70)

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MORTALITY IN INFLAMMATORY RHEUMATIC DISEASES

Causes of Death	All Death Cases <i>n</i> = 950	Rheumatoid Arthritis Death Cases <i>n</i> = 509	Spondyloarthropathies Death Cases <i>n</i> = 142	Systemic Connective Tissue Diseases Death Cases <i>n</i> = 299
Diseases of the circulatory system no, (%)	450 (47) *	257 (51)	51 (36)	142 (48)
Neoplasms including lymphopoetic system no, (%)	220 (23)	104 (20)	47 (33)	69 (23)
Diseases of respiratory system no, (%)	57 (6)	34 (7)	5 (3)	18 (6)
Diseases of the musculoskeletal system and connective tissue disease no, (%)	48 (5)	25 (5)	4 (3)	19 (6)
External causes of death no, (%)	38 (4)	17 (3)	10 (7)	11 (4)
Other diseases no, (%)	137 (15)	72 (14)	25 (18)	40 (13)

MORTALITY IN INFLAMMATORY RHEUMATIC DISEASES

Disease Entities	Meta-Standardized Mortality Ratio (95% CI) Including Current Study	Heterogeneity, Using I2 (%)
Rheumatoid arthritis (M05, M06)	1.44 (1.32; 1.56)	90.6%
Psoriatic arthritis (M07)	1.26 (1.08; 1.47)	74.0%
Ankylosing spondylitis (M46)	1.59 (1.29; 1.96)	57.1%
Systemic lupus erythematosus (M32)	2.65 (2.13; 3.28)	95.0%
Sjogren's syndrome (M35.0)	1.45 (1.13; 1.86)	87.0%
Systemic sclerosis (M34)	2.55 (1.76;3.68)	95.8%
Vasculitis (M30, M31)	1.92 (1.44; 2.57)	94.7%
Myositis (M33)	5.06 (3.67; 6.98)	89.6%
Polymyalgia rheumatica (M35.3)	0.95 (0.52; 1.73)	95.0%

MORTALITY IN INFLAMMATORY RHEUMATIC DISEASES

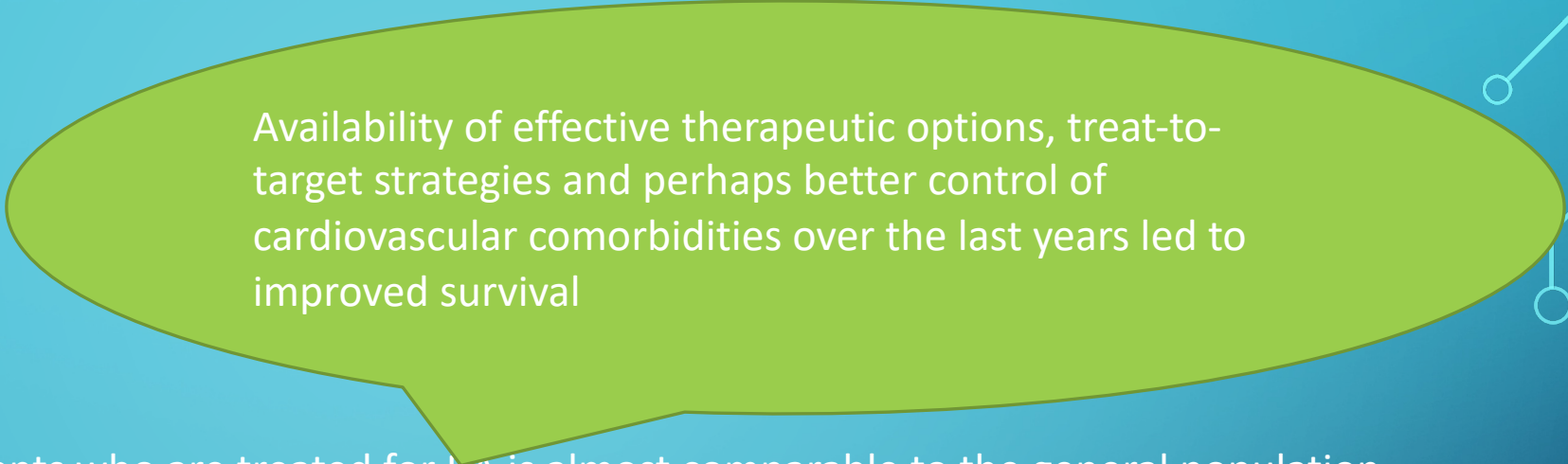
	RA		AS		PsA		SLE		SSc	
	Patients	General population	Patients	General population	Patients	General population	Patients	General population	Patients	General population
N	42 735	213 675	9707	48 535	13 779	68 895	10 440	52 200	2277	11 385
Female gender N (%)	33 641 (79)	168 205 (79)	4163 (43)	20 815 (43)	7565 (55)	37 825 (55)	9315 (89)	46 575 (89)	1998 (88)	9990 (88)
Median (IQR) age in years	64 (54–73)		47 (38–56)		54 (45–64)		53 (42–64)		59 (49–68)	

Bournia V-K, et al. *RMD Open* 2021;7:e001694. doi:10.1136/rmdopen-2021-001694

MORTALITY IN INFLAMMATORY RHEUMATIC DISEASES

The average effect of systemic rheumatic diseases on risk of death from all causes during a 5-year follow-up time, between 1 January 2015 and 31 December 2019

Variable	HR	95% CI	P value
RA	0.74	0.71 to 0.77	<0.001
AS	0.73	0.62 to 0.87	<0.001
PsA	0.78	0.70 to 0.87	<0.001
SLE	1.65	1.50 to 1.81	<0.001
SSc	2.72	2.33 to 3.17	<0.001



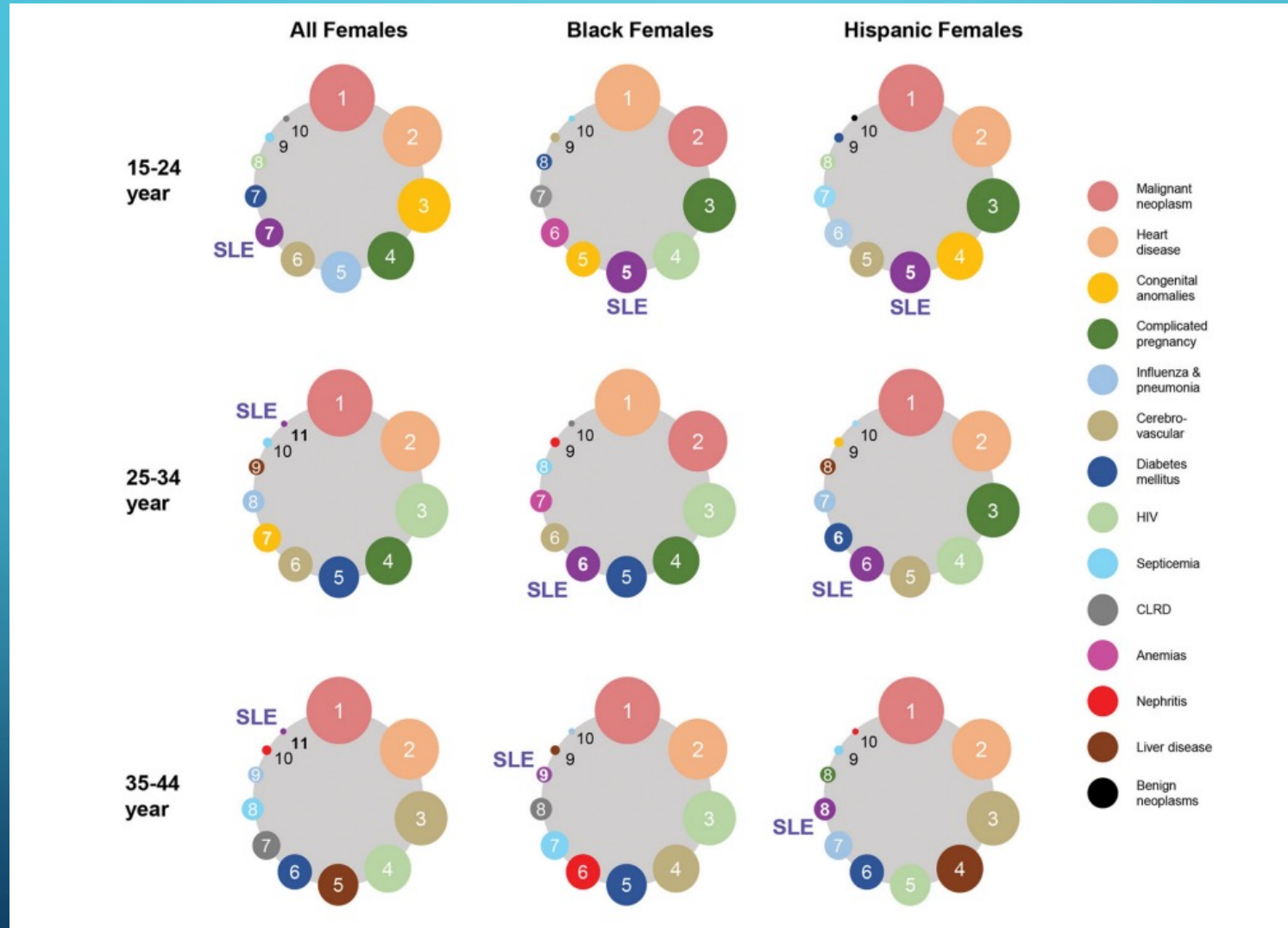
Availability of effective therapeutic options, treat-to-target strategies and perhaps better control of cardiovascular comorbidities over the last years led to improved survival

- All-cause mortality of patients who are treated for KA is almost comparable to the general population
- Patients with spondyloarthropathies, mortality rates are similar to the general population
- **Patients with SLE and SSc need closer follow-up and more effective treatments**

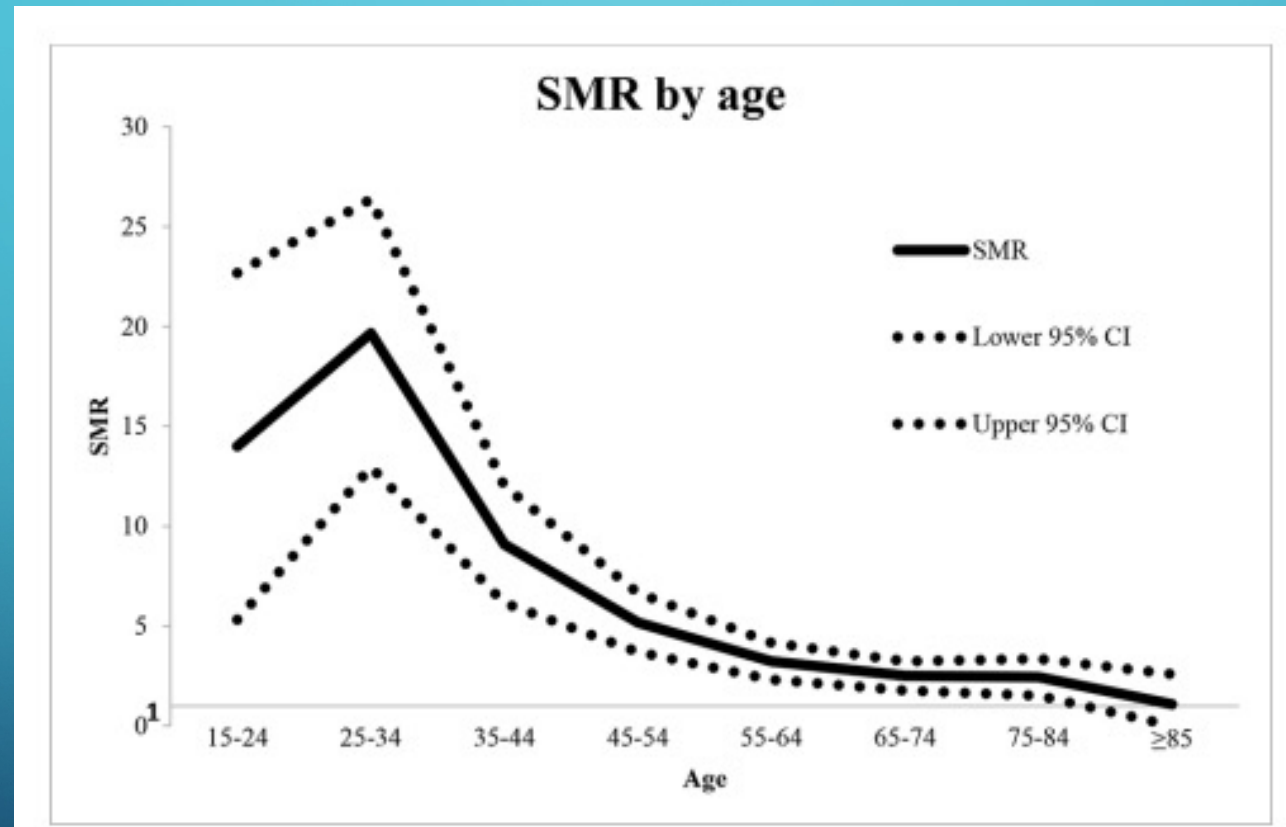
SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

- SLE is a chronic autoimmune disease of unknown cause that can affect virtually any organ of the body.
- Patients present with variable clinical features ranging from mild joint and skin involvement to life-threatening kidney, hematologic, or central nervous system involvement.
- Five- and 10-year survival rates for patients with SLE improved from less than 50% in the 1950s to more than 90% in the 1980s

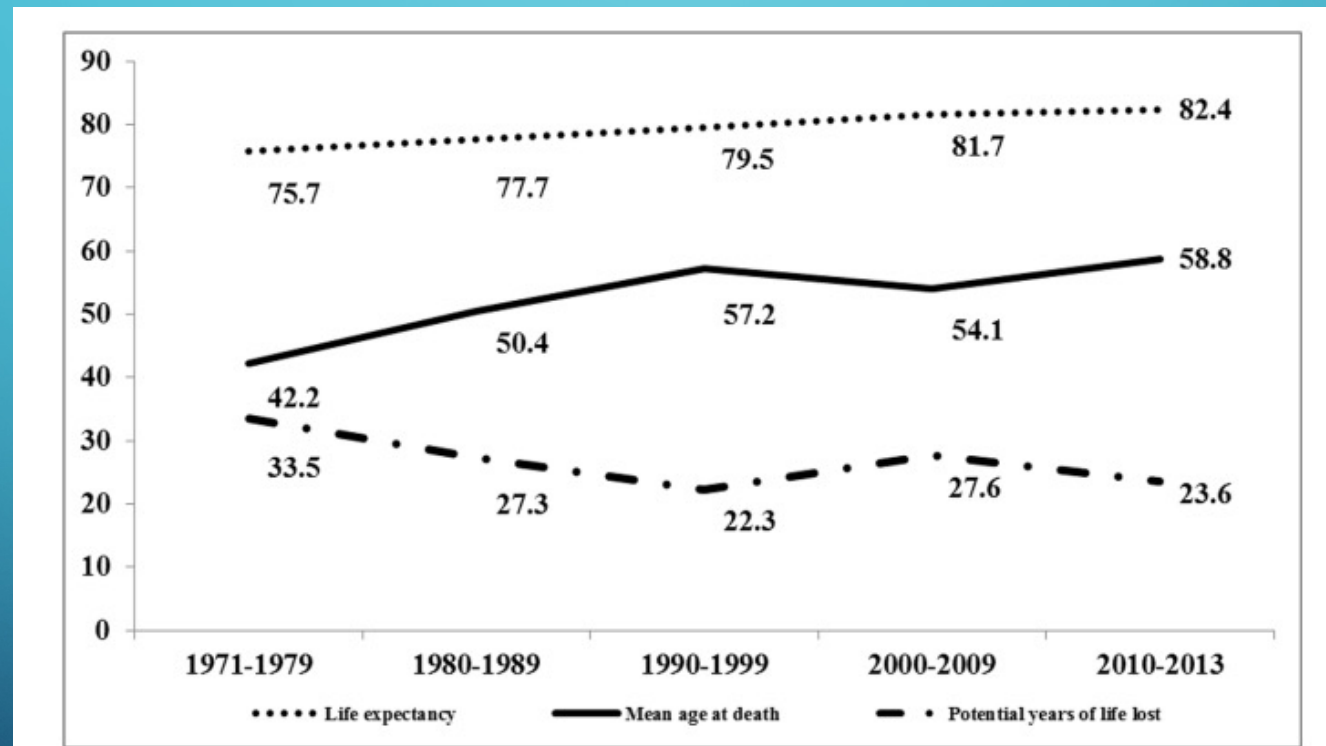
LEADING CAUSES OF DEATH IN FEMALES IN THE UNITED STATES FROM 2000 TO 2015



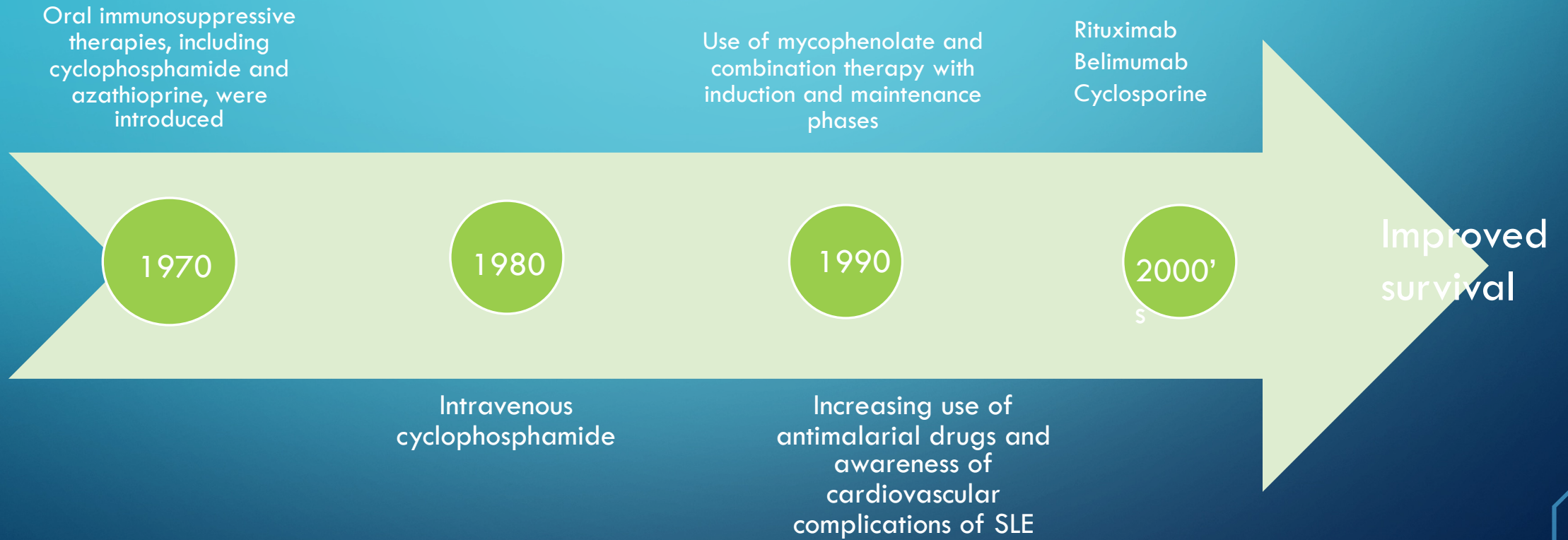
SLE MORTALITY



SLE MORTALITY



SLE MORTALITY



SLE MORTALITY IN US POPULATION

- Data from the U.S. National Vital Statistics System revealed that SLE mortality decreased in all subpopulations, including females and black persons, during the past decade
- Despite improving trends, SLE mortality remains high relative to non-SLE mortality, and disparities persist between subpopulations and geographic regions

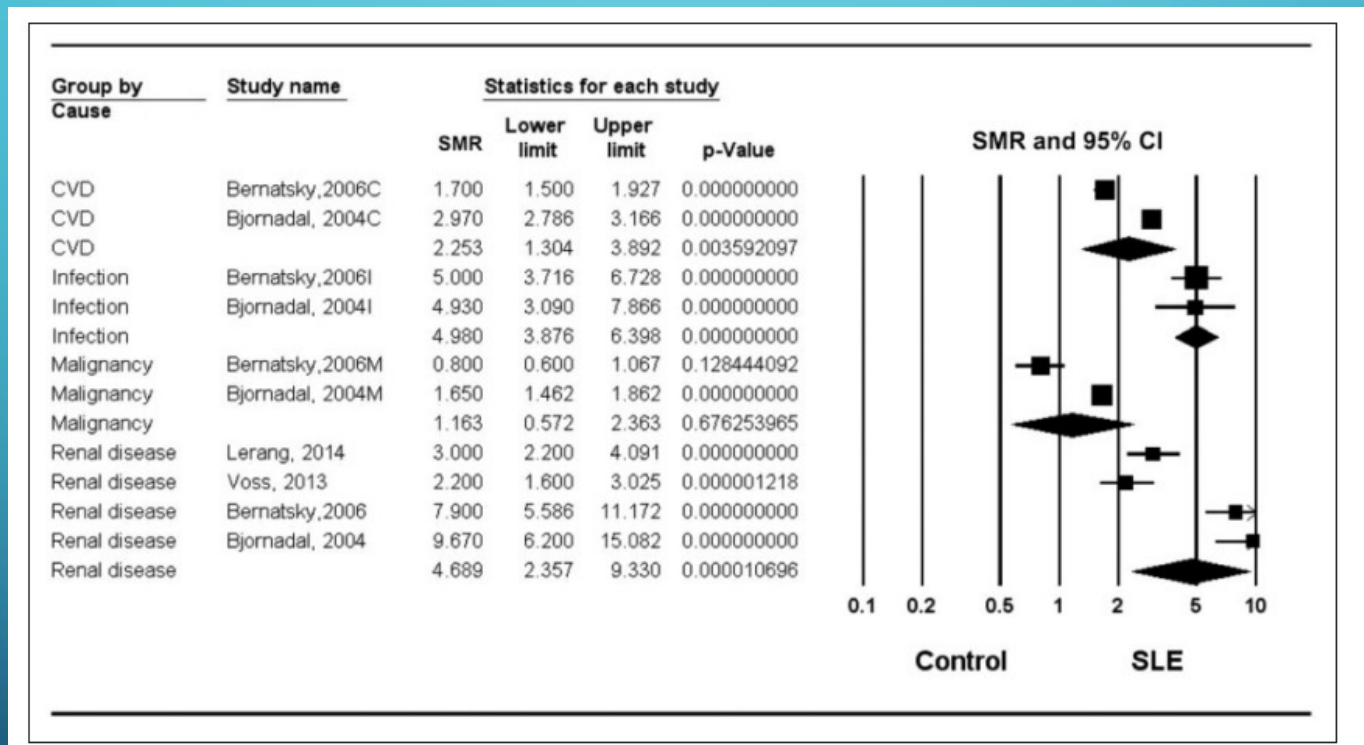
SLE MORTALITY IN US POPULATION

- Increased SLE mortality in older persons may be related to complications associated with increasing cumulative doses of immunosuppressive medications as well as SLE complications, such as atherosclerosis.
- Higher mortality in females might reflect the higher prevalence of SLE among them

SLE MORTALITY IN US POPULATION

- Increased SLE mortality in black persons might be attributable to more high-risk disease features, such as extensive cellular crescents in the kidneys
- Residence in the West conferred the highest SLE mortality risk in all racial/ethnic groups except white persons, who had the highest risk in the South.
- Clusters of elevated SLE mortality in Alabama, Arkansas, Louisiana, and New Mexico and clusters of low mortality in Minnesota, Vermont, Virginia, and Washington .
- The areas with elevated mortality had higher rates of poverty and/or greater concentrations of Hispanic persons than the areas with lower mortality

META-ANALYSIS OF CAUSE-SPECIFIC STANDARDIZED MORTALITY RATIO IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS.



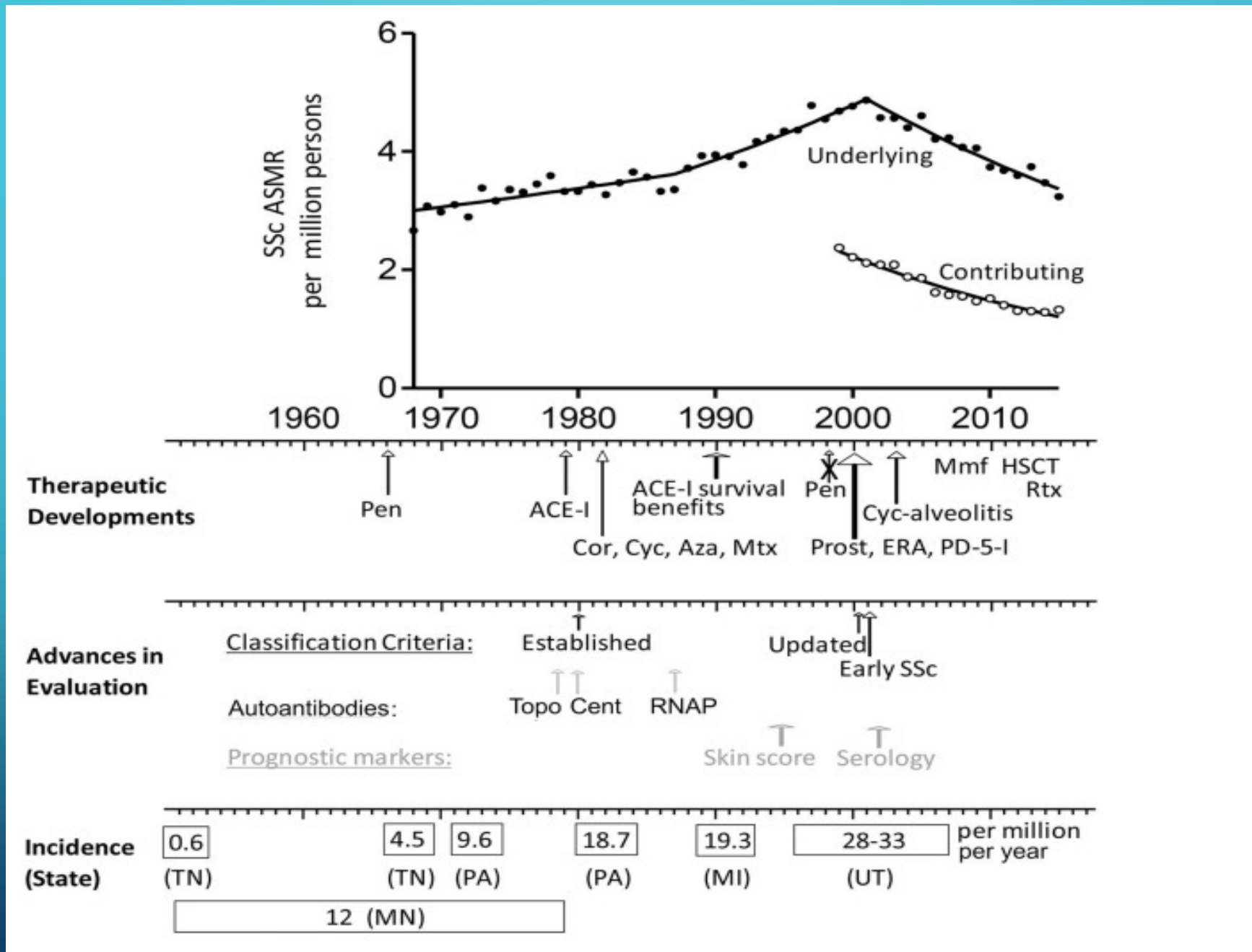
- Renal disease is associated with a 4.689-fold increase in mortality compared with the general population.
- Renal disease occurs in up to 60% of patients with SLE, and renal disease remains a predominant cause of morbidity and mortality in SLE.
- Twenty percent of patients with lupus nephritis develop end-stage renal disease at 10-year follow-up.
- Better management of renal disease in SLE may improve the ultimate mortality.

SYSTEMIC SCLEROSIS

- National mortality data compiled by the Center for Disease Control and Prevention's Wide-ranging Online Data for Epidemiologic Research, and population data from the United States Census Bureau was used to calculate age-standardized mortality rate (ASMR) for SSc and non-SSc (all other causes), and the ratio of SSc-ASMR to non-SSc-ASMR for each year from 1968 through 2015

SYSTEMIC SCLEROSIS

- Mortality attributable to SSc has steadily decreased in the last 1 ½ decade after 33 years of sustained increase from 1968 through 2000.
- Despite these 15 years of steady improvement, mortality rates for SSc relative to non-SSc were still higher in 2015 than in 1968.
- The rise-and-decline trend in SSc mortality may reflect changes in disease incidence, SSc recognition, improved evaluation, and/or better management,



SYSTEMIC SCLEROSIS

- The recent, steady improvement in systemic sclerosis mortality could have resulted from advances in the management of its complications, such as pulmonary hypertension and renal crisis.

RHEUMATOID ARTHRITIS

- Rheumatoid arthritis (RA) is the most common chronic form of inflammatory arthritis, affecting approximately 1 percent of the population
- F:M 2:1
- Nearly 40 percent of patients with RA will have work disability within 10 years of diagnosis

RHEUMATOID ARTHRITIS

- In the 1950's reports began to emerge that patients with rheumatoid arthritis (RA) were at increased risk of dying early
- Levels of premature all-cause mortality relative to the general population appear to be decreasing
- Cardiovascular risks remain elevated

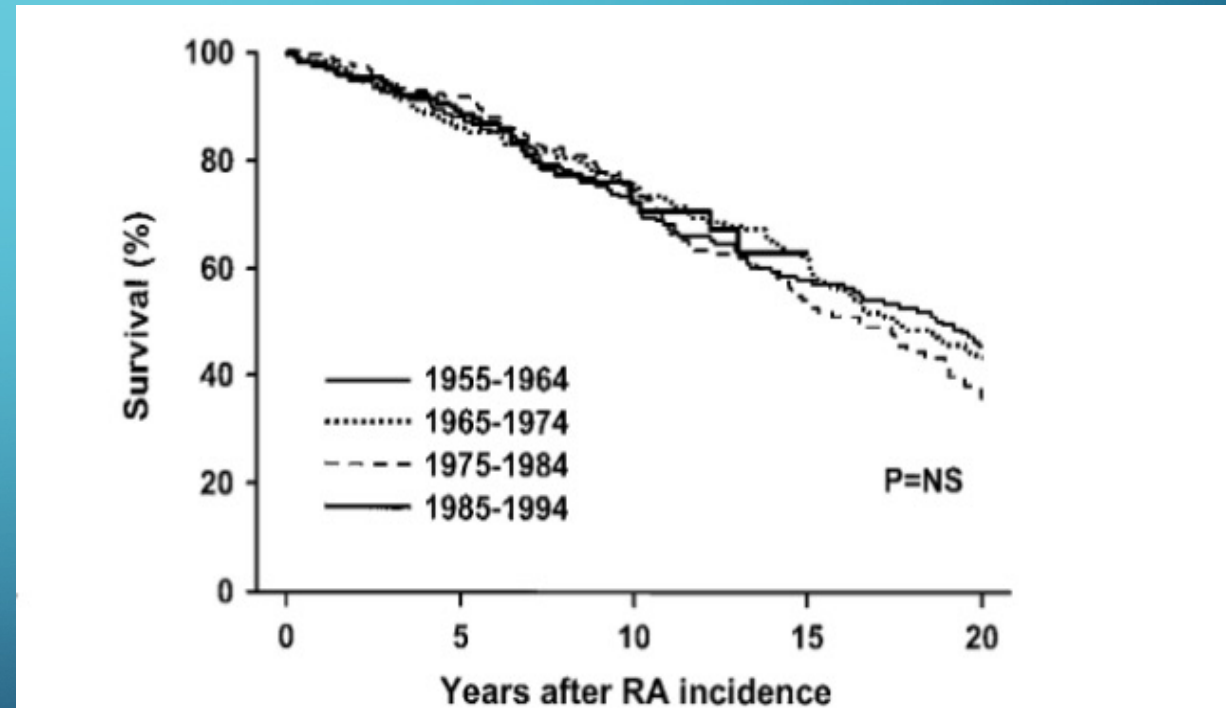
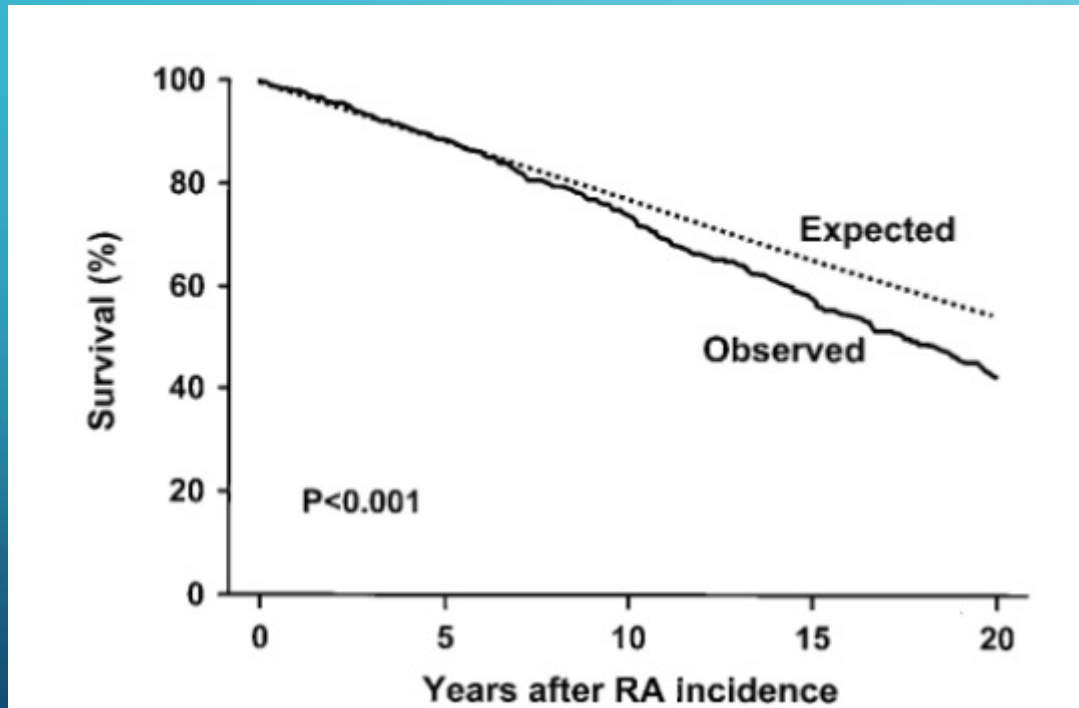
RHEUMATOID ARTHRITIS

- The first study of mortality in rheumatoid arthritis (RA), which appeared in 1953, reported an excess mortality of 29% among RA cases compared with control
- Inception cohort of all cases of RA first diagnosed between January 1, 1955 and December 31, 1994 among Rochester, Minnesota residents 18 years of age and older
- All cases fulfilled the 1987 American College of Rheumatology (ACR; formerly, the American Rheumatism Association) criteria for RA .
- Incidence date was defined as the first date of fulfillment of at least 4 of the 7 diagnostic criteria.
- All cases were followed up longitudinally through their entire medical records until death or migration from Olmsted County.
- All causes of death (including contributing causes of death) as reported in the medical record and/or the death certificate were collected for all cases

Rheumatoid arthritis

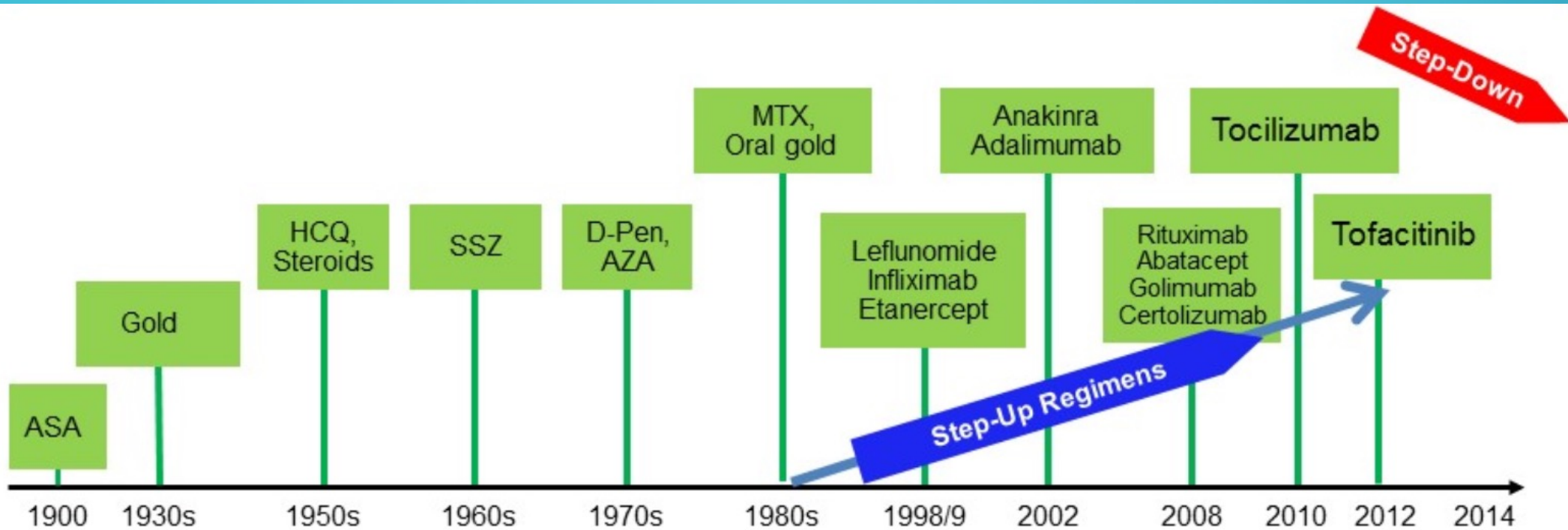
	Value
Number of patients	609
No. (%) female	445 (73.1)
No. (%) male	164 (26.9)
Length of followup, mean \pm SD years	14.2 \pm 9.4
Age at incidence, years	
Mean, median	58.0, 58.2
Minimum, maximum	18.5, 92.8
Incidence rate per 100,000 population (95% confidence interval)	44.6 (41.0–48.2)

RHEUMATOID ARTHRITIS



RHEUMATOID ARTHRITIS

- Survival in this RA cohort was significantly lower than that expected in the general population ($P < 0.001$) over the entire time period
- When compared with individuals from the same population of the same age and sex who did not have RA, patients with RA were at significantly higher risk of death, with an SMR of 1.27 (95% CI 1.13–1.41)
- Predictors of mortality:
 - Presence of > 1 extraarticular manifestations
 - Cancer with chemotherapy
 - History of alcohol use
 - Corticosteroid use

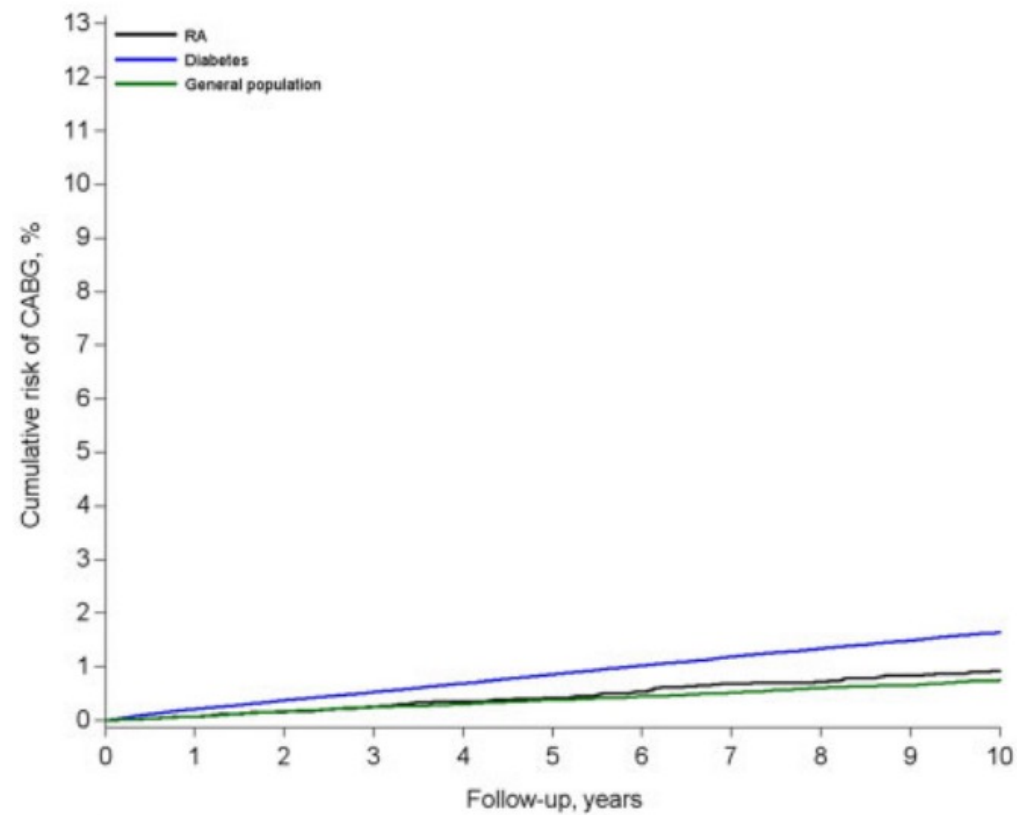
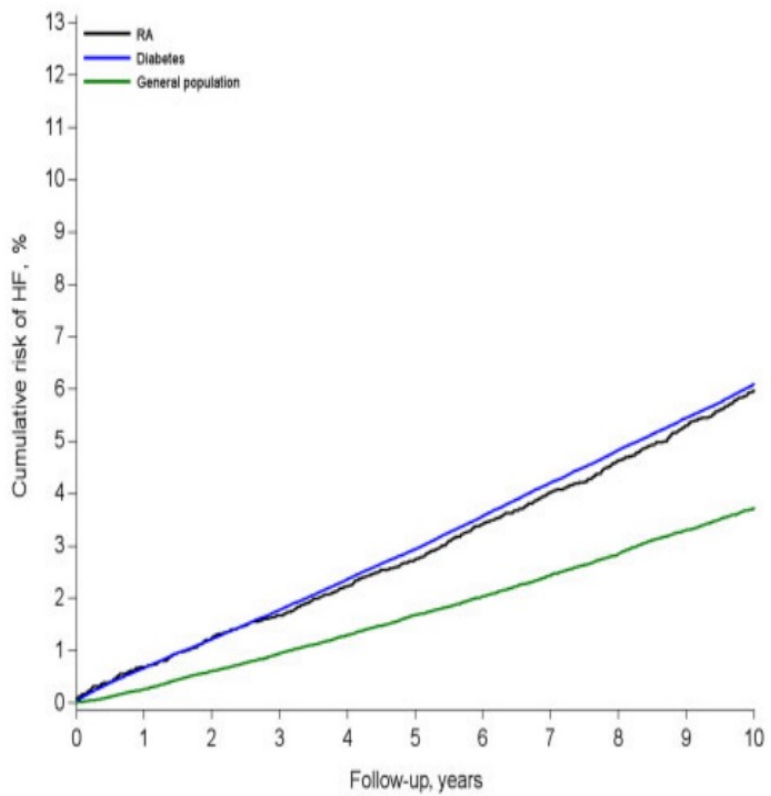


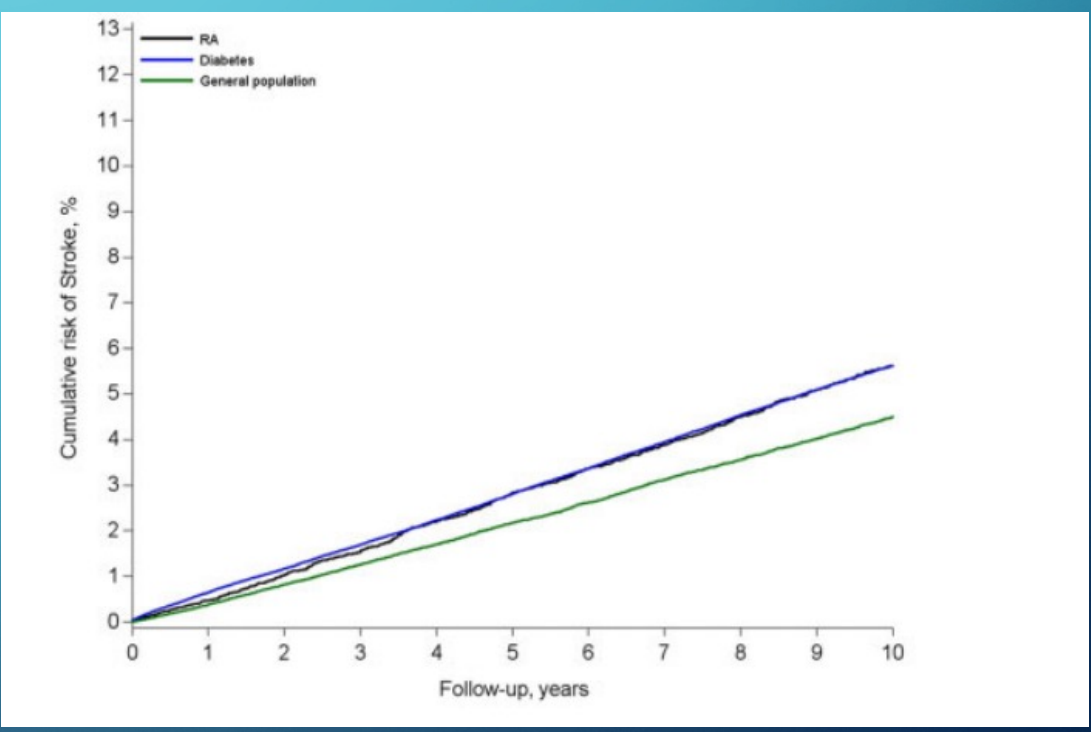
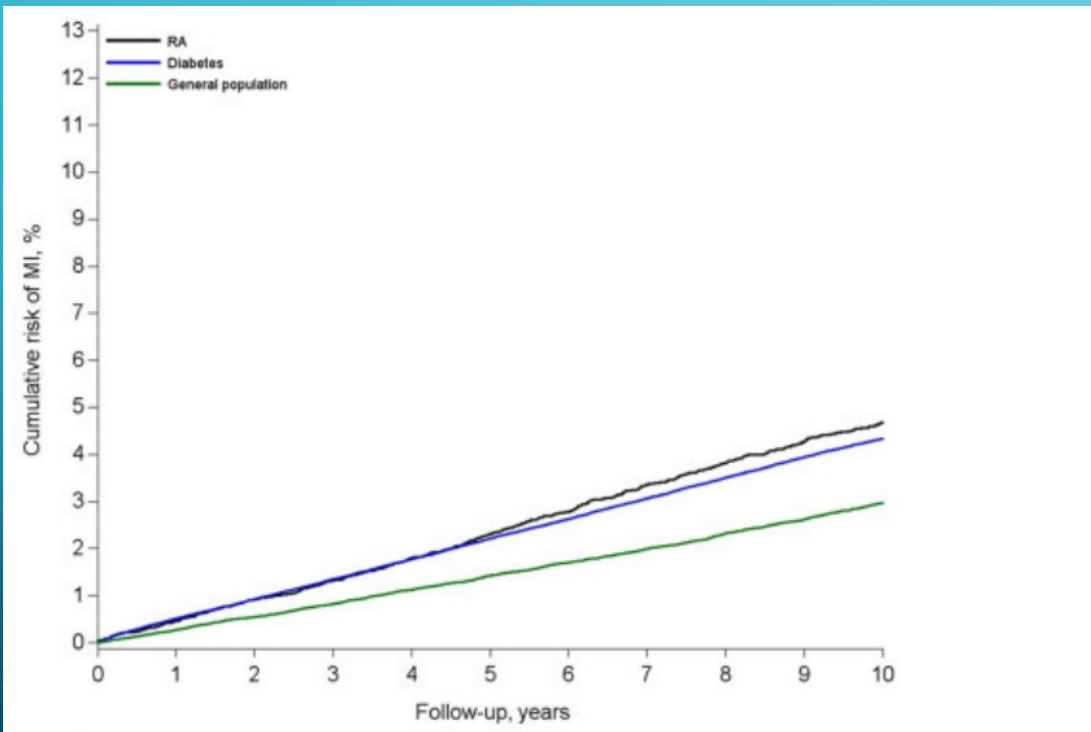
Treat Signs and Symptoms in Established Disease

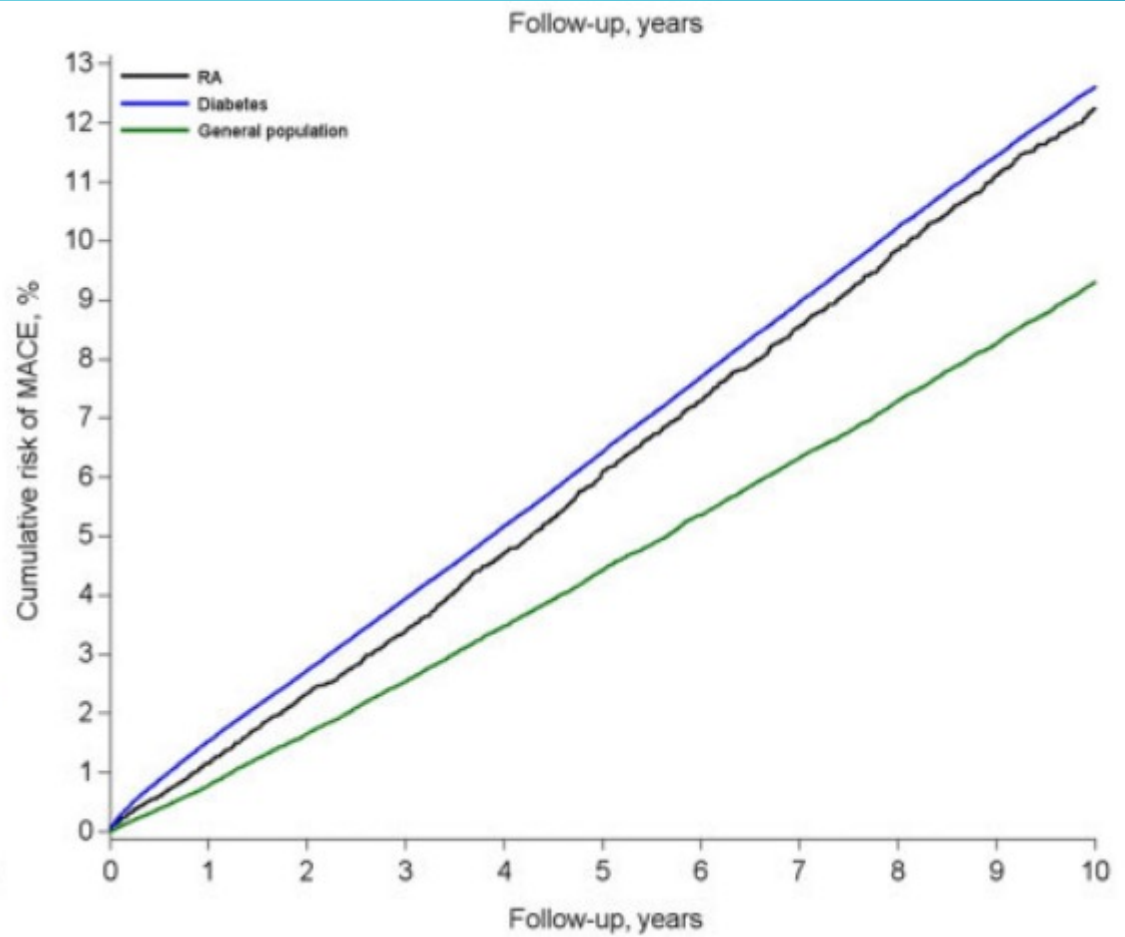
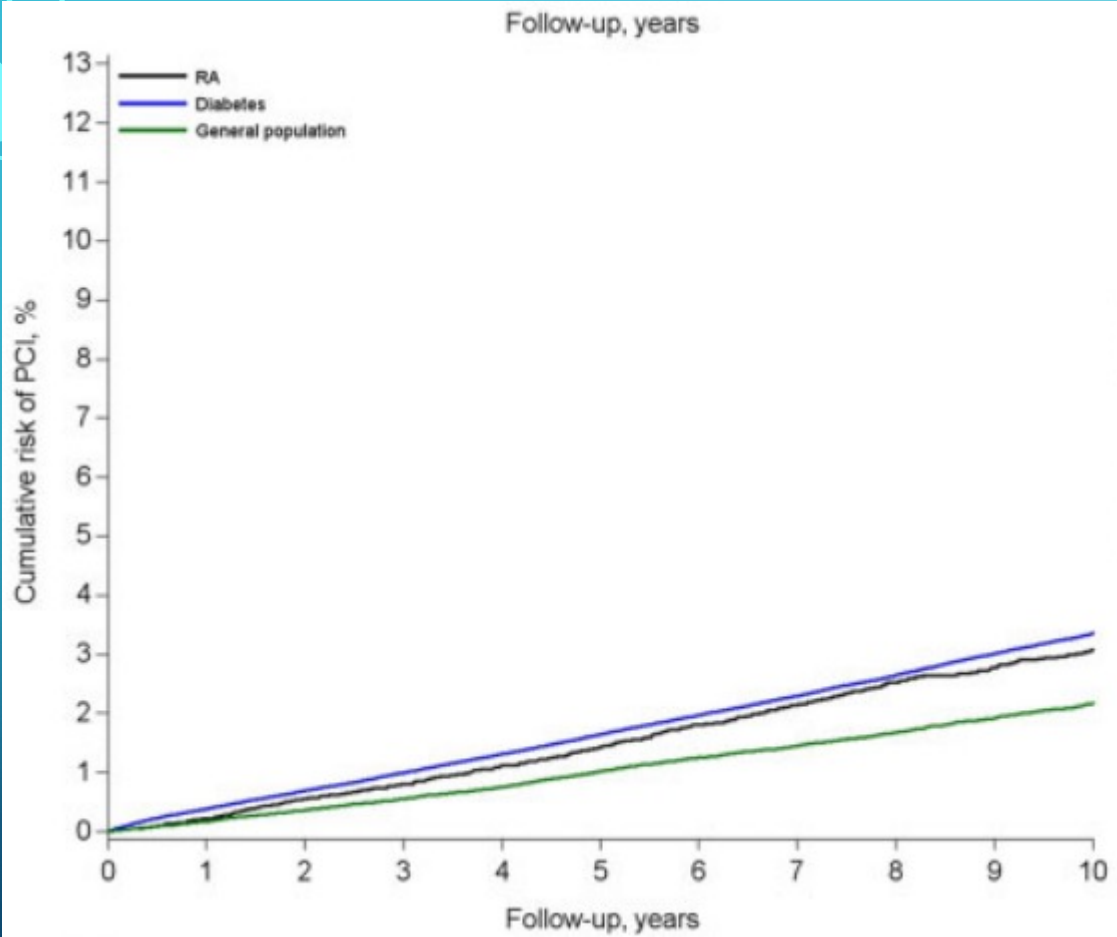
Combination and Biologic Rx Disease Modification

RHEUMATOID ARTHRITIS

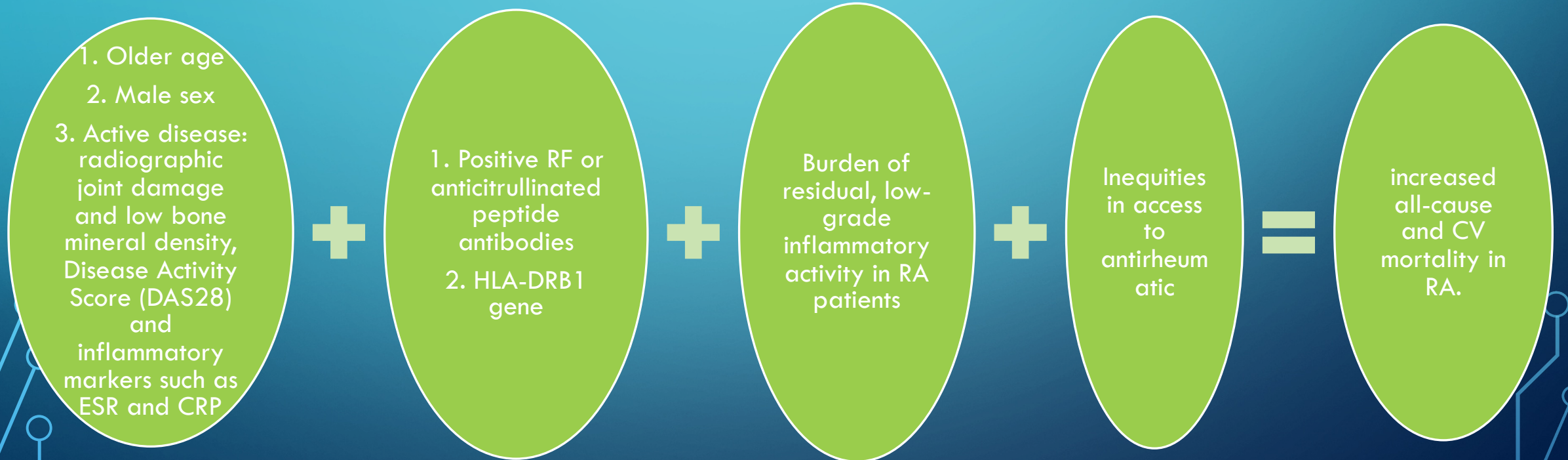
- 2021 report from Denmark, found similar 10-year all-cause mortality for patients with RA and the general population, but rates of cardiovascular disease remained higher among patients with RA and risk of MI that is comparable to patients with DM.







IMPACT OF INFLAMMATION, AUTOIMMUNITY, AND GENETIC DETERMINANTS ON INCREASED MORTALITY IN RHEUMATOID ARTHRITIS



ACCELERATED AGING IN RHEUMATOID ARTHRITIS: ARE WE READY FOR NEW TARGETS IN RHEUMATOID ARTHRITIS TREATMENT?

- Telomeric dysfunction and DNA instability leading to excessive apoptosis of T cells in patients have been recognized as key mechanisms of premature immune senescence in RA.
- Decreased functional competence in hematopoietic precursor cells (CD34+) in RA, independent of RA activity, suggesting impaired repair mechanisms associated with accelerated aging in RA patient
- Ability of TNF- α inhibitors to delay the onset of CD8+ T-cell senescence and to enhance telomerase activity in vitro

ACCELERATED AGING IN RHEUMATOID ARTHRITIS: ARE WE READY FOR NEW TARGETS IN RHEUMATOID ARTHRITIS TREATMENT?

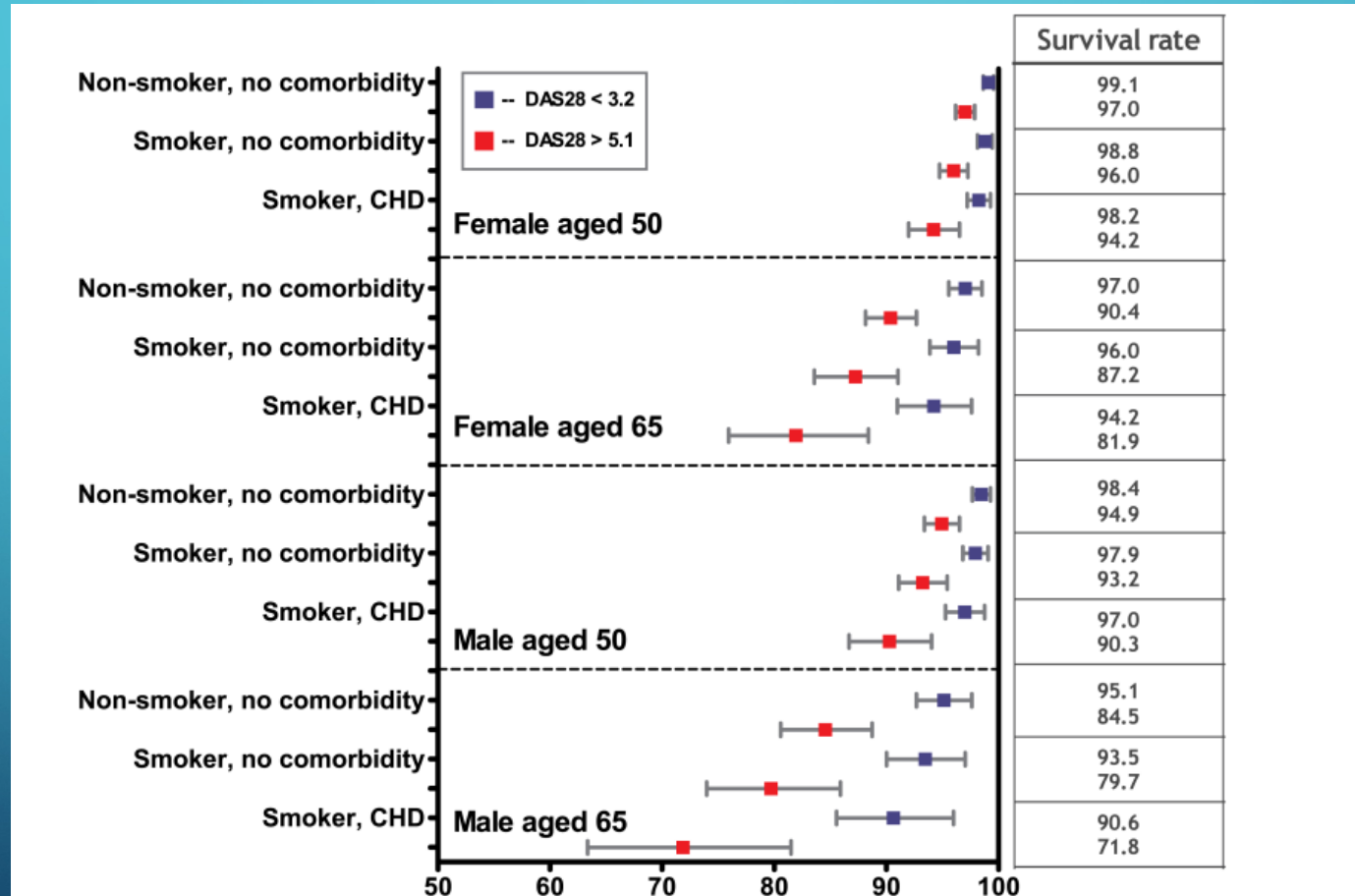
- Seropositive RA patients have already aged about 2 years more than their peers, and they continue to age at an accelerated pace during their disease course
- Disadvantaged pattern of morbidity and mortality whereby CV risk in individuals with RA equates approximately to the risk in individuals in the general population who are 5 to 10 years older
- The time of start, relation to immunologic changes, and its primary drivers, as well as the ways to control accelerating aging (ie, its potential prevention and/or reversibility)

IMPACT OF DISEASE ACTIVITY ON MORTALITY WITH RA

DAS28	Women		
	Deaths	SMR (95% CI)	Lost life years (95% CI)
<3.2	29	0.86 (0.58 to 1.24)	-1.5 (-3.0 to 0.0)
3.2-4.1	60	0.94 (0.72 to 1.22)	0.0 (-1.4 to 1.4)
>4.1-5.1	88	1.35 (1.09 to 1.67)	3.0 (1.1 to 4.9)
>5.1	132	3.33 (2.79 to 3.95)	10.3 (8.9 to 11.6)
Total	309	1.53 (1.37 to 1.71)	2.7 (2.0 to 3.4)

DAS28	Men		
	Deaths	SMR (95% CI)	Lost life years (95% CI)
<3.2	13	0.54 (0.29 to 0.92)	-2.4 (-6.1 to 1.3)
3.2-4.1	39	1.11 (0.79 to 1.52)	0.1 (-2.1 to 2.3)
>4.1-5.1	42	1.34 (0.96 to 1.81)	0.5 (-1.3 to 2.1)
>5.1	60	3.33 (2.54 to 4.30)	10.7 (8.9 to 12.6)
Total	154	1.41 (1.20 to 1.65)	1.9 (0.8 to 3.0)

IMPACT OF AGE, SMOKING, DAS AND CHD ON SURVIVAL RATE IN RA



	Unadjusted HR		Adjusted HR: 6 (rituximab 12) months risk window approach		
	HR	95% CI	HR	95% CI	p
At baseline					
Male	1.85	1.53 to 2.25	1.75	1.40 to 2.18	<0.0001
Age per 5 years	1.66	1.57 to 1.75	1.49	1.40 to 1.59	<0.0001
Diabetes	3.43	2.77 to 4.26	1.84	1.46 to 2.33	<0.0001
Chronic lung disease	3.31	2.63 to 4.17	1.68	1.31 to 2.17	0.0003
Chronic renal disease	4.90	3.71 to 6.47	1.94	1.43 to 2.63	0.0001
Prior malignancy	3.15	2.27 to 4.37	1.26	0.88 to 1.80	0.20
Osteoporosis	2.86	2.38 to 3.43	1.43	1.16 to 1.76	0.0015
Coronary heart disease	4.94	4.00 to 6.10	1.43	1.12 to 1.83	0.006
Smoker	0.82	0.62 to 1.07	1.37	1.02 to 1.85	0.038
At follow-up					
DAS28* <3.2	Ref.		Ref.		
DAS28* 3.2–4.1	1.81	1.21 to 2.71	1.15	0.76 to 1.74	0.49
DAS28* >4.1 to 5.1	2.29	1.57 to 3.33	1.17	0.78 to 1.75	0.43
DAS28>5.1	4.86	3.35 to 7.04	1.75	1.14 to 2.68	0.013
Prednisone most recent 12 months: 0 mg/d					
1–5 mg/d	1.33	1.00 to 1.76	1.05	0.80 to 1.38	0.71
>5–10 mg/d	2.22	1.65 to 2.98	1.46	1.09 to 1.95	0.013
>10–15 mg/d	3.95	2.61 to 5.98	2.00	1.29 to 3.11	0.0033
>15 mg/d	6.68	4.06 to 11.0	3.59	2.11 to 6.13	<0.0001
FFbH* in % of full function per 10% improvement	0.76	0.73 to 0.79	0.88	0.84 to 0.93	<0.0001
Methotrexate					
Other synth. DMARDs	2.53	1.95 to 3.28	1.14	0.86 to 1.51	0.36
TNF α inhibitors	0.77	0.61 to 0.98	0.64	0.50 to 0.81	0.0007
Rituximab	1.01	0.70 to 1.46	0.57	0.39 to 0.84	0.0062
TNF α inhibitors or rituximab	NA		NA		
Other biologics	1.02	0.68 to 1.52	0.64	0.42 to 0.99	0.043
DAS28>4.1 for > 6 (12) months after discontinuation of a biologic without start of a new one	NA		NA		

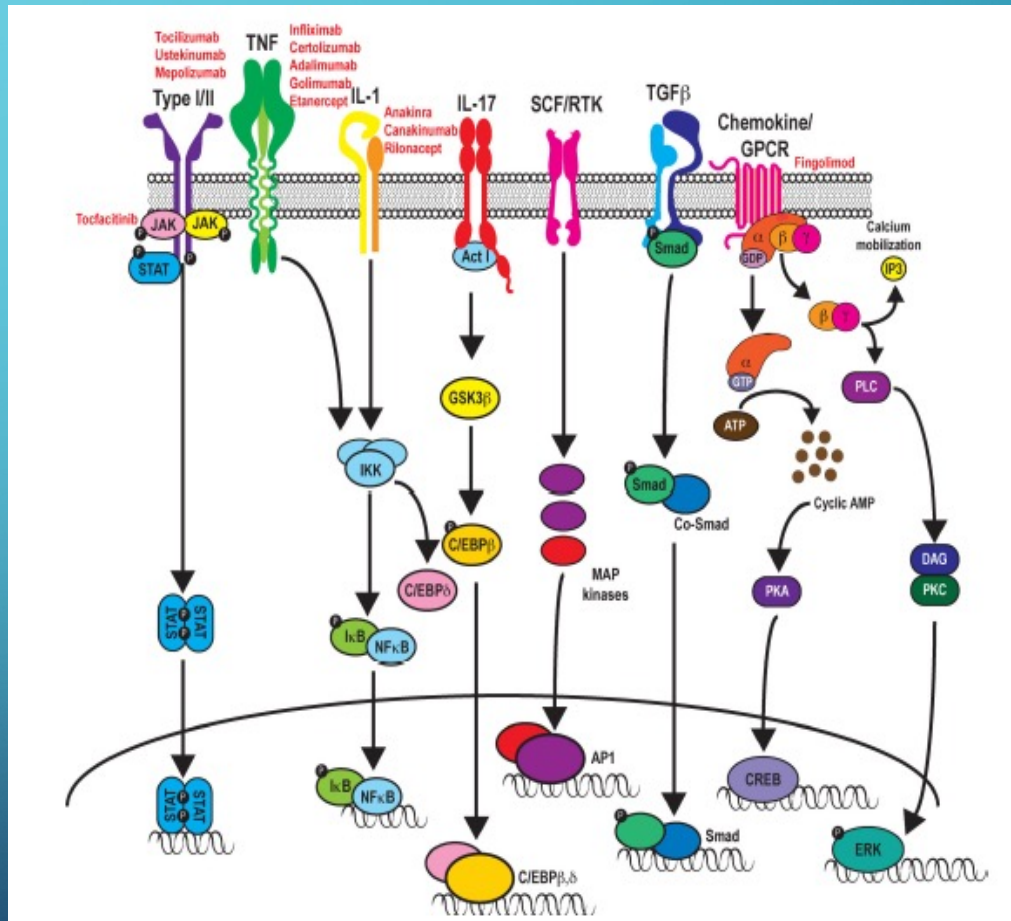
More attention should be paid to continuous monitoring and thorough targeting of inflammation in all patients to improve long-term outcomes of RA

OTHER ETIOLOGIES OF PREMATURE MORTALITY:

- Amyloidosis
- Transection of the cord due to cervical spine instability
- Respiratory failure due to interstitial lung disease

MODIFIABLE FACTORS

- Limit steroid use
- Counseling, smoking cessation
- Treat to target to achieve remission
- Treat traditional risk factors
- Recognize risk of depression and offer treatment



CLOSING THE GAP ON MORTALITY



Rheumatic Disease in America: Cost and Impact

52.5 million Americans are living with some form of rheumatic disease, including rheumatoid arthritis (RA), osteoarthritis, lupus, gout, scleroderma, ankylosing spondylitis, Sjögren's and juvenile idiopathic arthritis. Rheumatic diseases are the leading cause of disability in America and cost the U.S. healthcare system an estimated \$128 billion annually¹.

Rheumatic diseases are the leading cause of disability in America



The cost of rheumatic disease is expected to increase as the population ages



About the American College of Rheumatology

The American College of Rheumatology represents U.S. rheumatologists, rheumatology health professionals and the millions of U.S. patients living with rheumatic disease. We advocate for high-value, high-quality healthcare policies and reforms that will ensure safe, effective, affordable and accessible rheumatology care for our patients.

¹Barbour KE, Helrick CG, Davis KA, Murphy LB, Westman JM, Brady TJ, et al. Prevalence of Doctor-Diagnosed Arthritis and Arthritis-Related Disability Activity Limitation — United States, 2010–2012. *MMWR*. 2013;62(44):869-873. PMID: 24196662.

²Helrick CG, Felson DE, Lawrence RC. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. *Arthritis & Rheumatism*. 2008;50(1):15-25.

³Ibid.

⁴Ibid.

⁵WebMD E-Medicine Health website. (2011). Rheumatoid arthritis. Retrieved from http://www.emedicinehealth.com/rheumatoid_arthritis/article_em.htm. Accessed January 24, 2011.

⁶The Lupus Foundation website. (2011). Statistics on Lupus. Lupus Foundation of America. Retrieved from <http://www.lupus.org/about/statistics-on-lupus>. Accessed on May 2, 2011.

⁷Rheumatoid Arthritis. *New York Times*. <http://health.nytimes.com/health/guides/disease/rheumatoid-arthritis/overview.html>

⁸Centers for Disease Control and Prevention. National and state medical expenditures and lost earnings attributable to arthritis and other rheumatic conditions — United States, 2005. *MMWR*. 2007;56(1):4-7.

⁹Ibid.

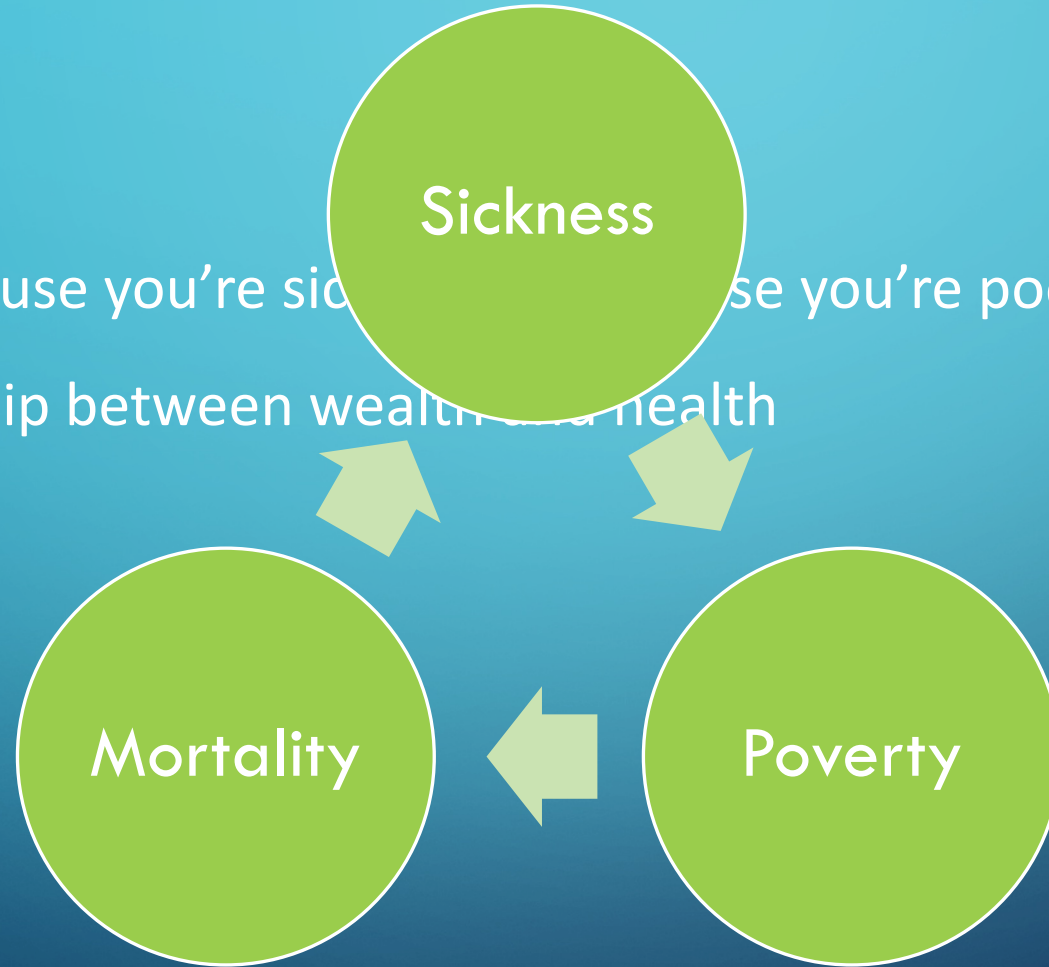
¹⁰Ibid.

¹¹Ibid.

¹²Ibid.

PUBLIC HEALTH FOCUS

- “Are you poor because you’re sick or are you sick because you’re poor?”
- Timeless relationship between wealth and health



PUBLIC HEALTH

We need to close the gap on poverty, mortality and health care disparities!

- Prevention of disabilities remains the primary focus of public health
- Acknowledge disabilities as part of the normal human experience
- Secondary focus of public health is the promotion of the health of persons with disabilities by identifying and closing reducible gaps between the health of persons with and without disabilities:
 - Eliminate health disparities
 - Reduce the socioeconomic disadvantages
 - Reduce structural barriers to the health system

